AN

INTRODUCTION TO MODERN THERAPEUTICS

BEING THE

CROONIAN LECTURES

ON THE

RELATIONSHIP BETWEEN CHEMICAL STRUCTURE AND PHYSIOLOGICAL ACTION

IN RELATION TO THE PREVENTION, CONTROL, AND CURE OF DISEASE.

DELIVERED BEFORE THE ROYAL COLLEGE OF PHYSICIANS IN LONDON, JUNE, 1889

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HIS FRIENDS

THOMAS R. FRASER

AND

OSWALD SCHMIEDEBERG

This Book

IS AFFECTIONATELY DEDICATED

BY

THE AUTHOR.

PREFACE.

SOME apology is required for the long delay in issuing this book, as, with the exception of a few additional woodcuts, it is a simple reprint of the Croonian Lectures, which were given three years ago at the Royal College of Physicians, and then appeared in the weekly Medical Journals.

The reason of the delay is partly that a few months after the lectures were delivered I was asked to go to India, to investigate the mode of action of chloroform, the Nizam of Hyderabad, at the suggestion of Surgeon-Major Lawrie, having most generously appointed a commission for the purpose.

But a more powerful reason of delay was simply the intention I had of extending the lectures so as to include the action of drugs on the function of the kidneys and other organs. In order to write this, I waited for a convenient season, but this has not come, and the pressure of other engagements seems to render it likely that I may have to wait some time before I can execute my intention; and therefore I have concluded to issue the book now without further delay.

I desire again to return my most sincere thanks to Sir Andrew Clark, Bart., President of the Royal College of Physicians, and to the other officers of the College for the honour they did me in appointing me lecturer, and the aid they gave me in carrying out my plan.

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Delivered June 27th, 1889.

CROONIAN LECTURES

ON THE

RELATIONSHIP BETWEEN CHEMICAL STRUCTURE AND PHYSIOLOGICAL ACTION.

LECTURE I.

PREVENTION OF DISEASE.

INTRODUCTION.

MR. PRESIDENT and Gentlemen,—Allow me, before commencing these lectures, to return you my most sincere thanks for the honour you have done me in asking me to deliver them, for the stimulus you have given me to collate the facts relating to a subject of the greatest practical importance, and for the substantial aid which you have afforded me in doing it.

The motto of this College, "Art is long and Time is fleeting," as it has been translated by Longfellow, is one which, while it tends to repress too sanguine expectations of individual success in furthering medicine, is yet a strong incentive to individual effort, and its teaching has been well put by the same poet in the words—

> "Let us, then, be up and doing,
> With a heart for any fate;
> Still achieving, still pursuing,
> Learn to labour and to wait."

The period of waiting on the advance of medicine has indeed been a long one, and in the Gulstonian Lectures which I had the honour to give in this place twelve years ago I tried to show to some extent why the progress of medicine has been so slow.

The Causes of Retardation.

Its advance has been mainly hindered, as I believe, because men have been guided in their practice more by their own fancies than by objective facts.* I expressed a hope that the advance of medicine would become more and more rapid as the knowledge gained by close study of objective phenomena became more and more the basis of our practice. I also ventured to echo the prediction made by Dr. B. W. Richardson in 1868,† that ere long we should be able to manufacture in our laboratories drugs which would produce in the animal body any effect that we might desire, without our having to obtain them, as one might say, hap-hazard from various plants or other sources.

Advance of Medicine and Surgery.

Already we owe a great deal to chemistry for the potent medicines which it has prepared and supplied to us.

Probably the two most striking advances which have been made in the healing art during the present century are the introduction of anæsthetics and of antiseptics.

Anæsthetics.

Anæsthetics have not only relieved the pains of labour and lessened the agony which occurs in various diseases coming within the province of the physician, but they have taken away the terror formerly associated with surgical operations, and have allowed the surgeon, in place of trying to finish his work in a few seconds, to spend minutes, or even hours, in doing the operations carefully and thoroughly.

They have thus not only made patients more ready to submit to surgical interference, but they have enabled the surgeon to attempt, and perform with success, operations which would formerly have been impossible.

Antiseptics.

The introduction of antiseptics has greatly lessened the spread of infectious diseases, and it has diminished the risk from surgical

* Lauder Brunton, "Gulstonian Lectures on Pharmacology and Therapeutics." (London: Macmillan and Co.)

† British Association Reports, 1868, p. 186.

operations to an extent that is almost incredible. The change it has produced may perhaps be best illustrated by the views which were taken a quarter of a century ago by one of the most eminent surgeons then living, as contrasted with those which prevail now. When I was a student I heard the late Professor Syme say with great emphasis, "Gentlemen, the operation of ovariotomy is not surgery; it is murder, and anyone who attempts to perform it should be hanged." Now, thanks to Professor Syme's son-in-law, Sir Joseph Lister, we see surgeons who are able to produce a hundred cases or more of consecutive operations of this sort, without a single death Once abdominal surgery was regarded as something which should be resorted to only when every other hope was gone, but now it is recognised to be little, if at all, more dangerous than operations on the limbs. By its aid life is now saved and health restored in cases where formerly the patient had nothing to look forward to but continual suffering, only terminated by certain and untimely death.

Introduction of New Remedies.

Another great advance which has been made, still more recently, is the introduction of various new antipyretics, some of which have not only the power of lessening fever, but of relieving pain.

At the present moment new drugs are being constantly introduced by the chemist to the notice of the physician, so rapidly, indeed, that it becomes a little difficult to keep *au courant* with all the recent introductions.

Most of the new drugs belong to one or more of three classes, viz., the class of antipyretics, of analgesics, or of hypnotics.

Several of them may be said to belong to all three classes at once, and will lessen temperature, relieve pain, and produce sleep; but generally one or other action predominates, and determines the class to which they are assigned, the other effects being more or less subsidiary or not existing at all.

These remedies are not taken hap-hazard from the innumerable substances known to the chemist, but are selected from certain groups, the members of which have been ascertained to possess the desired action in varying degrees.

OBJECT OF THESE LECTURES.

In these lectures I propose (1) to try and show what principles guide us in selecting new remedies from the enormous number of substances known to chemistry, and (2) to indicate the lines upon which further work is desirable, in order that we may be able to manufacture substances which will not only act upon any part of the body we wish to influence, but will produce upon it any particular effect we may desire.

In order to fulfil this twofold object I shall have to mention a number of facts already ascertained, but I shall be obliged also, in indicating the directions for future research, to introduce hypotheses which require to be tested by experiment and either proved or disproved.

The Prospects of Therapeutics.

The prospects of therapeutics appear to me very bright. At present most of the drugs which we are obtaining from the chemist belong to the classes of antipyretics, analgesics, or hypnotics, but I think it is highly probable that before long we shall have a series of drugs which will stimulate the biliary secretion of the liver or modify its glycogenic function, arranged in order of their comparative strength, in much the same way we have now the class of antipyretics. We may also look for a series of remedies which will modify the circulation by dilating the blood-vessels not only temporarily but more or less permanently, and will thus afford relief, not merely in transient conditions like angina pectoris, but in the prolonged high tension of chronic Bright's disease. We may also, I think, fairly expect to obtain a series of remedies having an action upon the heart and vessels, like digitalis, strophanthus, or erythrophlœum, and which will possess an advantage over these drugs in one most important point. For the chemical structure of the artificial cardiac tonics will be known to us, and we shall consequently be able to modify them, in the laboratory, in one way or another, until we secure the one which will have the particular effect desired in any given case.

We may also, I think, fairly expect to obtain a series of remedies which will act upon the spinal cord in such a way as to enable us to treat with success a number of diseases which are at

present almost altogether beyond the reach of our remedies. Our prospects of doing this are all the more hopeful, inasmuch as the introduction of antipyrin and other new remedies has already enabled us to relieve the pains occurring in some spinal diseases more efficiently than we were able to do before.

SUBJECT OF THE LECTURES.

The regulations of the Croonian Lectures have decided that they should be upon some subject in anatomy, physiology, or pathology in relation to the prevention, control, and cure of disease. My subject is a very wide one, for although it may be said to deal chiefly with physiology, it relates also to anatomy and pathology.

Development of Anatomy, Physiology, and Pathology.

All three subjects, anatomy, physiology, and pathology, as well as a new one, pharmacology, which may be looked upon as a subdivision of physiology, either have passed or are passing through similar stages in the course of their development.

Anatomy.

The old anatomists dealt with the organs and described the relationships of the bones and muscles, of the lungs and liver, without troubling themselves about their composition. From Bichat the study of anatomy received a new impulse, and the tissues of which the organs are composed became the subject of investigation. Next the anatomy of the tissues was taken up, and the importance of their constituent elements, the cells, was pointed out with regard to vegetable tissues by Schleiden, to animal tissues by Schwann, who has only recently passed away, and in pathological formations by Virchow, who, we rejoice to know, is still alive and active. The *anatomy of the cell* itself is now beginning to receive attention. The cell is coming to be regarded as "an elementary organism with the properties of a complicated organism," and the relationship of its different parts to one another is now examined with as much care as the old anatomists devoted to the relationship of the viscera.

Physiology.

Physiology has followed a similar course to anatomy, dealing

first with various functions, as related in a general way to the viscera, and afterwards with the functions of the tissues. But physiology, like anatomy, is now beginning to deal not merely with the functions of organs or tissues, but with the *functions of the cell.* It examines the phenomena of respiration, circulation, tissue change, motion, growth, reproduction, decay, and death in relation to single cells. Instead of the cell being regarded as a structureless mass of proteid matter, it is now considered to have a reticular structure, perhaps as complicated as the skeleton of one of the higher animals, with soft parts lying between which might be regarded as corresponding to the muscles and viscera. Instead of reproduction being a simple process of division, we now know that it is in many instances preceded by a most complicated series of movements within the cell, to which the name of *karyokinesis* is given, and which remind us of the movements which occur in a gas at the critical moment when it is condensing into a liquid, and are seen by passing a beam of light through it.

Pharmacology.

Pharmacology, like physiology, dealt first with the action of drugs upon general functions; and if we look into such a book as Orfila's Toxicology we find it noticed that after the administration of certain drugs the respiration was accelerated, enfeebled, or stopped entirely, the circulation was quickened or slowed, or that vomiting or purging occurred, without any reference to the mechanism through which these symptoms were produced. Magendie and Bernard did for pharmacology what Bichat did for anatomy, and began to localise the action of drugs to the tissues on which they act. The number of drugs to be investigated is so great, and the work required to do it is so laborious, that even now our knowledge of the exact mode of action of most of our drugs, and even of the most important of them, is far from complete, although a vast mass of information has been accumulated.

Cell Pharmacology.

Though much remains to be done in ascertaining the action of drugs upon organs and tissues, a new department of pharmacology is growing up—*the pharmacology of the cell*—corresponding

to its physiology. Indeed, without the pharmacology of the cell the study of its physiology would have been very limited, for even the highest powers of the microscope would not have enabled us to discover many of the most important points, both in structure and function, were it not that various aniline compounds have been found to affect differently the various parts of cells, and we have thus been enabled not only to observe the movements which occur within the cell, but to form some ideas regarding the activity of vital processes in its various parts.

Dr. Sheridan Delépine has made numerous observations on this subject, and has kindly furnished me with the following condensed account of the most important facts regarding it:—

"The most active part of a cell as far as essentially vital phenomena are concerned is undoubtedly the nucleus, and in the nucleus the part of the network which Flemming has called chromatin. The protoplasm of the cell, although practically undifferentiated in young or embryonic cells, and differing little from the nucleus, becomes with age distinctly differentiated by transformation into certain globulines, as in the case of muscle and of the crystalline lens, or by the accumulation within its meshes of various products, such as albuminoids, pigments, zymogenous substances, fats, calcareous salts, etc.

"Finally, some of these substances may either entirely replace the protoplasma, form a cell wall, or accumulate between the cells, and these masses of products of cell activity having lost all the properties of living protoplasm, can be considered as dead or differentiated to the utmost. The reactions of these various parts of tissues correspond to the physiological peculiarities just mentioned."

"Of the aniline dyes two great classes can be recognised—

(1) Acid fuchsin may be taken as a type of the first.

(2) Basic fuchsin as a type of the second.

The main difference between these two classes is that—

(1) The first class stains deeply the most differentiated parts of the cell.

(2) The second class stains deeply the least differentiated parts of the cell.

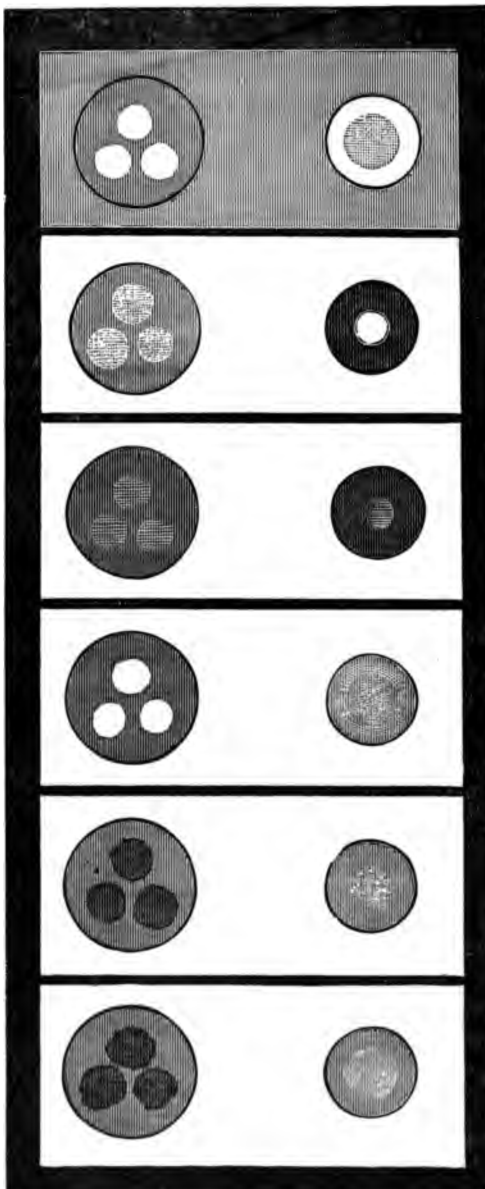


Fig. 1.—In this diagram the large circles represent leucocytes with enclosed nuclei. The small circles represent red blood corpuscles, and the space around both represents coagulated plasma. The nuclei may be regarded as the most actively living matter, the red corpuscles as the most differentiated and least actively living, while the body of the leucocyte is intermediate between them. The difference between the centre and periphery of the red corpuscle is supposed to only an optical effect.

Method of Staining—By drying a film of blood on a cover glass, fixing by absolute Alcohol for 5 minutes, and leaving for 5 minutes in the stain, 1 in 30 (30 per cent. Alcohol).

SUMMARY OF OBSERVATIONS MADE BY DR. SHERIDAN DELÉPINE ON THE AFFINITY OF VARIOUS TISSUES OR PARTS OF TISSUES FOR CERTAIN DYES.

A.

1. Living protoplasma does not stain readily, under ordinary circumstances, with most of the dyes studied (viz., acid magenta, eosin, magenta, methyl-aniline violet).

2. Interstitial fluid or products which are found in the midst of the protoplasma of certaiu cells may stain, but the colour is generally discharged after a short time, indicating active chemical changes taking place in the cell.

3. Just before death a number of parts begin to stain, but the substances which thus stain seem to be interstitial products (and paraplasma ?).

4. Immediately after death (often less than 1″ or 2″) the cytoplasm and the nucleoplasm stain.

(Result of observations made on intusoria and several rotifera.)

B.

1. The affinity of tissues for certain compounds seems to bear no distinct relation to some of the physical properties of the latter, such as colour, but is distinctly influenced by their chemical properties. But there seems to be a distinct relation—

(1) Between the amount of carbon contained in the radical of the stain and its affinity for the tissues (if one is careful to compare only the compounds belonging to the same type).

(2) There is also some relation between the amount of nitrogen entering with the compound and its staining properties, but the effect seems to be the reverse of that which is produced by the carbon.

(3) Some of the dyes which behave like acid aniline dyes have very different affinities from those which act like bases.

2. The dyes must form some very loose compounds with the various parts of the tissues, and there must be, in some cases at least, a difference between the compounds formed with one form of tissue and another; for when dyes such as methyl-aniline violet, magenta, acid magenta, eosin, and others are used, not only is there a marked difference in the intensity of the stains, but there may be as many as two, three, and even four shades obtained; that these shades are not due to structure only is shown by the difference of action of the various stains.

Thus, if a drop of blood after proper treatment be stained by acid fuchsin the red corpuscles will be intensely stained, the substance of the leucocytes very faintly stained, the nuclei not stained at all.

If, on the contrary, *basic fuchsin* be used the nuclei will be stained most deeply, the body of the leucocytes stained less, the red corpuscles least of all."

Diagram to show Relation of Differentiation with Affinity for—

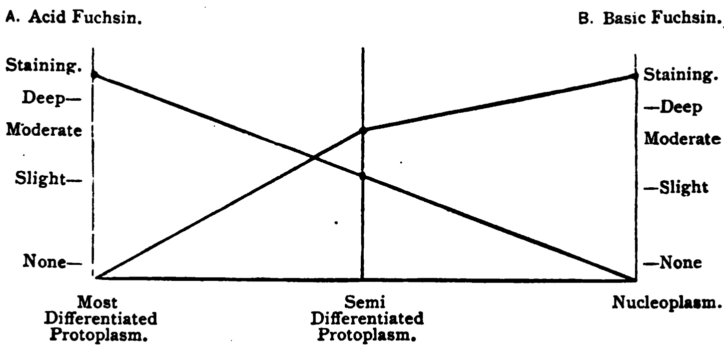


Fig. 2.

In the case of the aniline colours we can see that different cells or different parts of the same cell exercise a selective power, taking one and refusing another. It is probable that the same thing occurs in the case of other substances which we cannot see under the microscope, and that strychnine, for example, unites with the cells of the spinal cord rather than with those of bone cartilage or muscle.

What I have just called selective power is no doubt in many instances merely a chemical attraction between the components of the cell and the chemical substances brought in contact with it, for it occurs after the cell is dead. It resembles the apparent selective power of the grains of gold dust in the process of amalgamation, for when mercury is mixed with powdered quartz, sand, and gold the other substances remain unaffected, and it only combines with the gold. In other instances it may possibly be connected with the life of the cell, and at all events the alteration in colour which some of the aniline colours undergo

when oxidised or reduced also renders visible to the eye the chemical changes which occur in the cell, and allows us to observe its respiratory functions, in the same way as the redness or blueness of the comb in a fowl, or of the nails or mucous membranes in a man, indicates the arterial or venous character of the blood and the completeness or imperfection of the respiratory functions in the fowl or the man.

Pathology.

Turning to pathology, we find a similar development occurring as in the kindred sciences of anatomy and physiology.

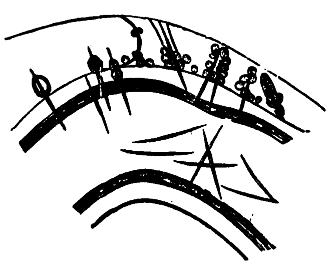


Fig. 3.

A piece of the anterior part of the body of a Daphne with a number of Spores, some of which are still in the intestinal canal; others are penetrating the intestinal wall, and others are free in the abdominal cavity, where they are attacked by Leucocytes. The cells which eat up others are termed Phagocytes. This and the following figures are after Metschnikoff.

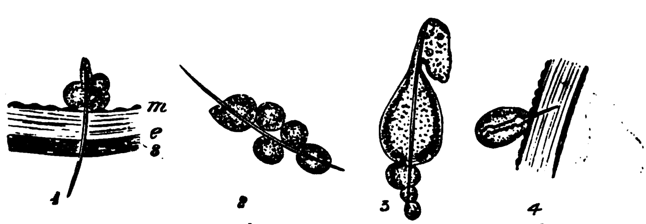


Fig. 4.

a, a Spore which has penetrated the intestinal wall and entered the abdominal cavity, where four Leucocytes have surrounded its end. *b* and *c*, Spores surrounded by Leucocytes, which have become confluent in *c*. *d*, a Spore, one end of which is being digested by a Leucocyte.

Morgagni described the seats of disease in the organs; Virchow

investigated pathology as depending upon the cells; Cohnheim threw a new light upon the process of suppuration by observations on the movement of wandering cells; and the researches of Metschnikoff on digestion within cells, both wandering and fixed, form a new point of departure for investigations on the relation between living organisms and infective diseases.

Fig. 5.
Different stages of the digestion of Spores by Phagocytes.

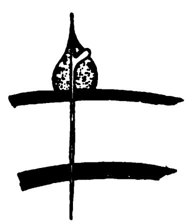
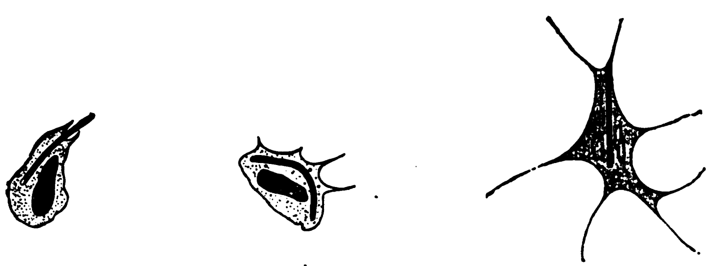


Fig. 6.
A germinating Spore with Leucocyte adhering to it.



a *b* *c*

Fig. 7.
a, Leucocyte of a Frog eating up an Anthrax Bacillus. *b*, the same Leucocyte after it has completely enveloped the Bacillus. *c*, a connective tissue Phagocyte containing three Fungi Cells.

We have not succeeded in tracing all infective diseases to micro-organisms, and it is possible that further researches may

even modify the views now commonly held with regard to the relation of microbes to disease.

Phagocytes and Microbes.

The phenomena which Metschnikoff has observed may not be of such universal occurrence as he has supposed, but nevertheless they probably play an important part in the struggle against disease.

Fig. 8.

A Spore germinating and forming Conidia, which drop off and become free in the abdominal cavity.

a *b* *c*

Fig. 9.

a, *b*, *c*, Stages in the process of a Leucocyte eating up Conidia.

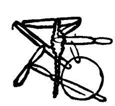


Fig. 10.

A group of Conidia which have caused the Leucocytes surrounding a Spore to dissolve, leaving only an empty vesicle and fine detritus.

From them we see that a likeness may be observed between the body corporeal and the body corporate, and that the death of a mouse from anthrax may be compared with the destruction of the Roman Empire by the savage hordes who invaded it. The anthrax bacilli, after invading the organism, enter into conflict with the cells belonging to it, and if the invaders be few and weak they are destroyed, and the organism preserved; but if the invading

bacilli are numerous and powerful they destroy the cells which they encounter, and death of the organism is the result.

Sometimes, instead of completely overmastering and destroying the organism into which they enter, the microbes appear to make only a local settlement, where they interfere with the growth of the cells of the part attacked, and may either lead to their destruction or may possibly induce them to take on a new manner of growth,* and thus lead to the formation of local tumours or local mischief of other kinds.

Nature of Cancer.

In many instances we are able to trace disease directly to the introduction of microbes from without, but occasionally, as in cancer, we find the cells of the organism itself take on an independent action, and grow in a manner not only independent of the interests of the organism as a whole, but so as actually to destroy it. The question is a natural one, What causes the cells of the morbid growth to take on this peculiar action? and some have sought to answer it by looking in the cancer for some microbes which had induced the disease, as the ovum of an insect leads to the production of galls in the oak. The success of this search is as yet uncertain, and the statement that the bacillus of cancer has been discovered must be confirmed by further observation before it can be definitely accepted, but it is not improbable that ere long the nature of cancer may be finally determined, and thus by-and-by lead up to the discovery of a cure for that dreadful disease.†

Influence of Heredity.

We sometimes speak of disease as hereditary, but this is not strictly correct. The tendency to the disease is no doubt hereditary, but the disease itself is not, at least in those cases where it is due to a microbe. Such diseases require two factors for their occurrence, just as a crop of grain does for its growth. The first factor is the microbe, which may be regarded as the seed, and the

* Nægeli, *Arch. f. exp. Path. u. Pharm.*, Bd. xix., p. 101.

† Kubdsoff, "Proc. of 3rd Gen. Meeting of Russian Med. Men at St. Petersburg," 1889, No. 2,141, abstracted in *Brit. Med. Jour.*, March 23, 1889, p. 665.

second is a condition of the organism which we may compare to the soil suitable for its reception. The soil is hereditary, but the seed may or may not be sown in it; and just as a field without the seed will produce no crop, however good the soil may be, so if the microbes be absent disease will not occur, however great the susceptibility of the individual may be. For example, we not unfrequently speak of the hereditary nature of consumption. Yet we are constantly meeting with persons belonging to very consumptive families who escape the disease by living under conditions where the bacillus tuberculosis is likely to be absent. On the other hand, persons, such as nurses, are in all probability frequently inhaling the microbe, and yet are not attacked by the disease. In the first case immunity is probably due to the absence of the seed, notwithstanding the favourable nature of the soil; in the second it is probably due to the barrenness of the soil, notwithstanding the presence of the seed. But just as the seed falling on a soil adapted to its growth will germinate and yield a crop, so microbes which find within an organism conditions suitable to their growth will multiply and cause disease.

As two factors are required for an attack of infective disease, viz., a disease germ and a suitable soil, it is evident that we may try to prevent it either by destroying the germ or by rendering the soil unsuitable. Both plans are now largely employed, but the consideration of them belongs to a later division of these lectures.

Life Processes in Disease Germs and in the Human Body.

In these lectures I have, in accordance with the regulations of the College, to consider my subject in relation to the (1) prevention, (2) control, and (3) cure of disease. I may be able, to a certain extent, to treat these three separately, but the last two—the control and cure—are so intimately connected that it is almost impossible to separate them completely.

I have already mentioned that many diseases depend upon the invasion of the organism by microbes, and in discussing the action of chemical agents in the treatment of disease we must consider their effect upon both factors, viz., the organism and the microbes.

We were formerly accustomed to look upon mankind as entirely different and quite apart from the rest of the animal kingdom, but ideas have entirely changed, and we now see that in the lowest organisms, even in those microbes which are such potent causes of disease, the processes of life are not unlike those which go on in the human body. In both we have nutrition, respiration, growth, reproduction, decay, and death. These functions are dependent both in man and microbes upon substances which may not always have exactly the same composition, but which are essentially of a proteid nature.

Concerning Protoplasm.

The name protoplasm has been a household word ever since Huxley's famous lecture in 1862, but since that time, when he sketched out with a master's hand the great features of protoplasmic life, manv details have been filled up by laborious investigators.

Protoplasm is able to absorb and disintegrate various substances which it uses for its own nutrition. Within its substance respiratory functions are performed, oxygen being absorbed, and carbonic acid being eliminated, and by the energy thus liberated the protoplasm may move about, or may carry on processes of chemical synthesis, and build up complex chemical substances from simple materials.

The waste products of its tissue change are excreted, and just as the poor captives in the Black Hole of Calcutta were poisoned by the respiratory products they had themselves formed, so the lowest organisms will be destroyed if the products of their own tissue waste accumulate sufficiently around them.

"*Extractive Matters.*"

The best-known products of tissue waste in man are carbonic acid, urea, and uric acid, but in old books on the chemistry of the urine one constantly met with the expression "extractive matters." This term was used to indicate the smeary mass, resembling a vegetable extract, which remained on evaporation of the urine after the urea and uric acid had been removed. These extractive matters have now been more fully examined, and in them

recent investigators have discovered powerful poisons. Indeed, the amount of poison excreted by a man in four-and-twenty hours is frequently so great that it would have been sufficient to kill him if injected into his veins at once.*

Amongst the products of tissue change in low organisms have been found a number of substances which destroy these organisms, or which, in other words, are antiseptic. Amongst these are phenol, phenyl-acetic acid, cresol, indol, phenyl-propionic acid, and skatol. These are not all equally powerful as antiseptics, for phenol, better known as carbolic acid, is weakest, the others becoming progressively stronger, in the order just mentioned.†

Apology for the Elementary Character of Some Parts of these Lectures.

In the list of products of the tissue change of microbes there are three names—phenol, phenyl-acetic acid, and phenyl-propionic acid—whose similarity of sound suggests a relationship to one another, but many men will not understand the nature of this relationship, either because they have forgotten the chemistry of these substances, or perhaps have never known it. For chemistry is a very young science, very little over a hundred years old, and a knowledge of the phenyl compounds is one of its newest acquisitions. The question what antiseptics have the greatest power to destroy the microbes, and are at the same time least injurious to the human organism, is one of vital importance. And yet if I tell you that bodies containing a diphenyl nucleus are amongst the most powerfully antiseptic, and at the same time least poisonous substances, many of you might reply by asking me, "What is diphenyl?"

On the other hand, it is quite possible that many, especially of the younger Fellows of this College, who have studied chemistry recently, may laugh me to scorn for attempting to explain what is as simple to them as A B C.

But it was my misfortune to study chemistry in the old days when one spoke of equivalents, and atomic weight was not heard

* Bouchard.

† Wernick and Salkowski, *Virchow's Archiv*, 1879, vol. lxxviii., p. 51.

of. In trying to keep up, even to a very limited extent, with the progress of the science, I have had not only a great deal to learn, but a good deal to unlearn. The difficulties I have had in understanding the subject have made me try as far as possible in the present lectures to give such brief information regarding modern chemical ideas and facts as may be helpful to those who have had the same difficulties as myself, and I trust that those whose more recent and fuller knowledge renders such an attempt useless to them will nevertheless forgive me for making it.

Course followed in the Lectures.

I know it is almost impossible to apprehend many statements reregarding the relation of chemical substances by simply hearing them once. I also know that although it may be little more than a waste of time and a tax upon your patience to make such statements in a lecture, yet without a knowledge of chemical relationships it is impossible for you to understand the subject of which I am treating. I have therefore resolved to follow a middle course, and to put down a number of relationships in the form of tables, to which either you or I can refer at will, without being under the necessity of going over them from end to end. (*Vide* Appendix.)

But while they will save me from going into details, there are some general considerations into which I must enter in order to render my subject at all intelligible to those who, like me, had the misfortune to learn chemistry long ago, and whom other engagements have prevented from keeping up with its progress.

Division of Chemical Substances into Organic and Inorganic.

The composition of the universe was formerly regarded as very simple, its component elements being only four—viz., fire, air, earth, and water. Now we regard as elements some sixty odd substances, and we give them this title because we cannot split them up by the means at our disposal. But it is possible that new methods may effect their decomposition, and then they will lose their title, just as potash did when Davy succeeded in showing it to be composed of oxygen and a metal, and it was accord-

ingly removed from the class of elements to that of compounds. The substances which we at present regard as elements, numbering between sixty and seventy, form by their union with one another an innumerable host of compounds. These used to be divided into two great groups—viz., organic substances, which were supposed to owe their origin to life, and inorganic, which had no such origin. Many organic substances can now be manufactured in the laboratory, and so the old reason for their name no longer exists, but all living things, however high or low they may be in the scale of creation, contain carbon, and the name organic is now retained for compounds of carbon, and inorganic for compounds of other elements.

ORGANIC MATTER THE BASIS OF LIFE.

Darwin described the evolution of the higher forms of life from the lower, and Lockyer and Crookes have described the evolution of the elements from primitive matter. But there is still a great gap between the elements and organic matter, and another between organic matter and living matter. The evolution of organic matter has still to be described, for we require its presence on the earth before we can have life at all.

In another place* I have discussed the various beliefs regarding the origin of living things, but first of all there must be organic matter. For if we take the Mosaic account of the formation of animals from the dust of the ground we still want the organic dust. If we assume that living things were gradually developed out of highly complex organic elements upon the earth itself, or suppose, with Sir William Thompson, that the germ of life was brought hither by a meteor from some distant planet, we still require the presence of complex organic matter in order to form the protoplasm, which was to serve as a physical basis for the life which was gradually developed in it, on the one supposition, and which was implanted, took root, and spread, on the other.

PROTOPLASM.

The highly organised protoplasm which forms the physical

* Lauder Brunton, "The Bible and Science." (London: Macmillan and Co.)

basis of life has in all probability a most complicated chemical structure, and Pflüger supposes that the relation which the size of a protoplasmic molecule bears to that of an ordinary chemical molecule is like that of the sun to the smallest meteor. We do not know how this gigantic molecule is built up, but we are learning something about its component parts by a study of the substances which it yields when decomposed. Amongst these products of decomposition we find various acids containing carbon, and compounds in which nitrogen plays an important part. If we subject any living matter to great heat we find that it becomes charred, showing us the presence of carbon as one of its most important constituents, while the unpleasant smell indicates the presence of nitrogen. The more powerful the decomposing agencies to which protoplasm is subjected, the more simple are the compounds into which it falls, until it is reduced to the elements themselves, or to some of their simplest combinations.

Evolution of the Elements.

It will probably facilitate our study of chemical structure if we begin at the very beginning, and take the genesis of the elements themselves before we proceed to the compounds which they form. But it must always be borne clearly in mind that our hypotheses on this subject refer only to the *how*, and not to the *why*—to the mode of making, and not to the Maker.

Darwin and Lyell have taught us to look for the explanation of a natural phenomenon to regular sequences of a similar kind, and we shall probably be right if we assume that the combinations by which new substances are formed in the present day are not altogether unlike the processes by which the elements themselves were evolved, although the conditions of temperature are, of course, utterly different. At any rate, it will, I think, help us if we take a look at the mode in which the elements are supposed to have been evolved, and I will try to repeat to you as nearly as possible the simple words in which Mr. Lockyer described his hypothesis to me. His view is still regarded by many as a mere hypothesis, yet, like Dalton's atomic theory, it may be most useful in

enabling us to string together known facts, as well as indicating the way to search for others yet unknown.

Let us suppose the universe to be filled with atoms of matter, each one like the other. By-and-by some of them coalesce, forming groups of two amongst the majority of single atoms. While some of the twos remain as they are, others, meeting single atoms, form groups of three, and others, meeting double atoms, form groups of four. Aggregation goes on unceasingly, until we have single atoms, groups of two, three, four, and five atoms, and so on. Moreover, differences will occur in these groups according to the way in which the atoms are aggregated together, for some may be joined lineally to each other, while others form

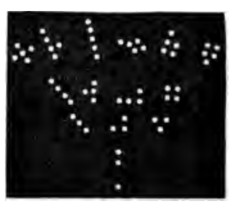


Fig. 11.

Diagram to illustrate Lockyer's hypothesis of the evolution of the elements.

cubes, triangles, or irregular clumps, as shown in the accompanying diagram. Thus we may have groups of the same atomic weight, with quite different properties. The elements combine to form meteoric dust, the dust to form meteors, and the meteors to form stars and solar systems.

Let us now fill in this bold outline of the evolution of the elements as given by Mr. Lockyer with more detail, and I cannot do it better than by quoting extracts from Mr. Crookes' address at the British Association in 1886. Premising that in the diagram

which he has most kindly lent me the vertical line represents temperature slowly sinking through an unknown number of degrees,

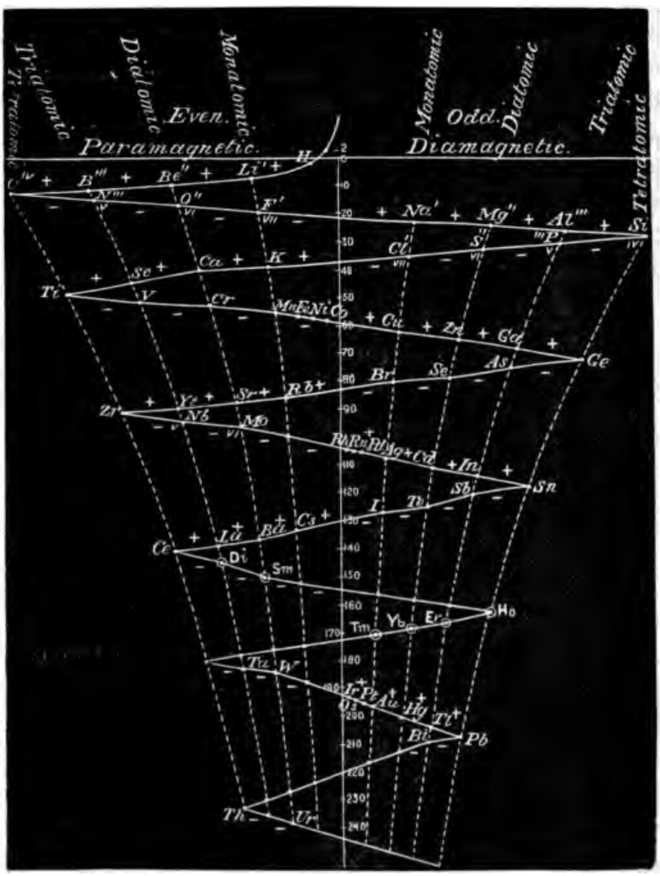


Fig. 12.

The Genesis of the Elements.

and that the oscillating line, swinging to and fro like a mighty pendulum, is intimately connected with electricity, he says—

"Let us start at the moment when the first element came int

existence. Before this time matter, as we know it, was not. It is equally impossible to conceive of matter without energy as of energy without matter; from one point of view the two are convertible terms. Before the birth of atoms all those forms of energy which become evident when matter acts upon matter could not have existed—they were locked up in the *protyle* as latent potentialities only. Coincident with the creation of atoms, all those attributes and properties which form the means of discriminating one chemical element from another start into existence fully endowed with energy. The pendulum begins its swing from the electro-positive side; lithium, next to hydrogen in simplicity of atomic weight, is now formed; then glucinum, boron, and carbon. Definite quantities of electricity are bestowed on each element at the moment of birth; on these quantities its atomicity depends, and the types of monatomic, diatomic, triatomic, and tetratomic elements are fixed. The electro-negative part of the swing now commences; nitrogen appears, and notice how curiously position governs the mean dominant atomicity. Nitrogen occupies the position below boron, a triatomic element, therefore nitrogen is triatomic. But nitrogen also follows carbon, a tetratomic body, and occupies the fifth position counting from the place of origin. How beautifully these opposing tendencies are harmonised by the endowment of nitrogen with at least a double atomicity, and making its atom capable of acting as tri- and pentatomic. With oxygen (di- and hexatomic) and fluorine (mon- and heptatomic) the same law holds, and one half oscillation of the pendulum is completed. Again passing the neutral line, the electro-positive elements, sodium (monatomic), magnesium (diatomic), aluminium (triatomic), and silicon (tetratomic), are successively formed, and the first complete oscillation of the pendulum is finished by the birth of the electro-negative elements, phosphorus, sulphur, and chlorine; these three, like the corresponding elements formed on the opposite homeward swing, having each at least a double atomicity depending upon position. Let us pause at the end of the first complete vibration, and examine the result. We have already formed the elements of water, ammonia, carbonic acid, the atmosphere, plant and animal life, phosphorus for the brain, salt for the sea, clay for the solid earth, two alkalies, an alkaline earth, an earth, together with their carbonates, borates, nitrates, fluorides, chlorides, sulphates, phosphates, and silicates, sufficient for a world and inhabitants not so very different from what we enjoy at the present day."

He then continues, "Lower and lower the temperature falls,

heavier and heavier grow the molecules, until uranium is reached, with a molecular weight of 240.

"What comes after uranium? I should consider that there is little prospect of the existence of an element much lower than this. Look at the vertical line of temperature slowly sinking from the upper to the lower part of the curve; the figures representing the scale of atomic weights may be also supposed to represent inversely the scale of a gigantic pyrometer dipping into the caldron where suns and worlds are in process of formation. Our thermometer shows us that the heat has been sinking gradually, and, *pari passu*, the elements formed have increased in density and atomic weight. This cannot go on for an indefinite extent. Below the uranium point the temperature may be so reduced that some of the earlier formed elements which have the strongest affinities are able to enter into combination among themselves, and the result of the next fall in temperature will then be, instead of elements lower in the scale than uranium, the combination of oxygen with hydrogen, and the formation of those known compounds the dissociation of which is not beyond the power of our terrestrial sources of heat."

EVOLUTION OF ORGANIC MATTER.

Amongst the compounds of which Mr. Crookes speaks we may include those formed by the combination of carbon with hydrogen, oxygen, and nitrogen, as well as compounds of these latter elements amongst themselves. That carbon may have very different physical characters we can see at a glance by comparing the three forms in which we are acquainted with it—

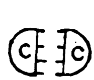


Fig. 13.
Diagram of a Charcoal Molecule, consisting of Two Atoms united by Four Affinities of each.

diamond, graphite, and charcoal. There seem to be differences quite as great in its atomic characters. Each atom appears to

have four affinities, and these may unite either with four atoms of another element having only one affinity each, or all four affinities may unite with those of another atom of carbon, forming a molecule of carbon, such as we have in charcoal, with no free affinities at all. Between those conditions we have various intermediate stages, in which the carbon atoms are united to one another by three affinities, two affinities, or one affinity respectively, while the other affinities remain free for combination with other elements. The simple experiment of throwing a piece of egg into the fire or of lighting a jet of gas shows us that complicated compounds of carbon cannot exist at a high temperature. Consequently organic matter could not exist on this earth until a comparatively late period in its history, when it had cooled down greatly from its original condition of intense heat. But let us suppose that the temperature has fallen sufficiently to allow compounds of hydrogen and carbon to exist. In the diagram to which I have referred Mr. Crookes looks upon electricity or something akin to it as one of the great factors in the evolution of the elements.

FORMATION OF CARBON COMPOUNDS.

Open Chain Compounds—Acetylene.

Now, if sparks be passed from carbon point to carbon point while they are surrounded by an atom of hydrogen a new compound will be formed, to which the name of *acetylene* has been given. In it the carbon atoms, instead of being united to one another by all their four affinities, as in the charcoal of which I have just spoken, are united to one another only by three, so that each atom has one free affinity by which it can combine with an atom of hydrogen, thus :

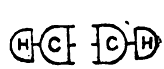


Fig. 14.
Diagram of Acetylene.

or thus : H—C≡C—H.

Ethylene—Methane.

Suppose that acetylene thus formed were to meet with nascent hydrogen, the affinities by which the carbon atoms were linked would be diminished first to two, and then to one. The affinities thus set free would combine with hydrogen to form ethylene, $^{H}_{H}{>}C = C{<}^{H}_{H}$, and then methane, or marsh gas, $^{H}_{H}{>}C{<}^{H}_{H}$.

Ring Compounds, Benzene, etc.

You will notice that in the three substances just mentioned, acetylene, ethylene, and methane, that the carbon atoms unite like the links of an open chain, and these bodies all belong to one of the great classes into which carbon compounds can be divided, the so-called fatty or alcoholic series, because oils, fats, and alcohol belong to it. But when acetylene is strongly heated the carbon atoms unite in another way, so as to form a closed chain, in which the carbon atoms of acetylene are supposed to have, as it were, opened out their connecting affinities, so that no two are connected by three affinities, or bonds as they are often termed, but are alternately connected by two, as in the accompanying figure. Three molecules of acetylene unite to form one of benzene, and this substance, in which the six atoms of carbon form a close ring, or nucleus as it is termed, is a type of the second great class of carbon compounds, the aromatic series.

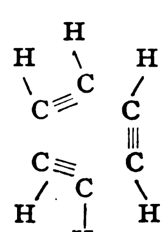


Fig. 15.

Diagram of Three Molecules of Acetylene.

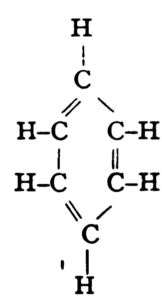
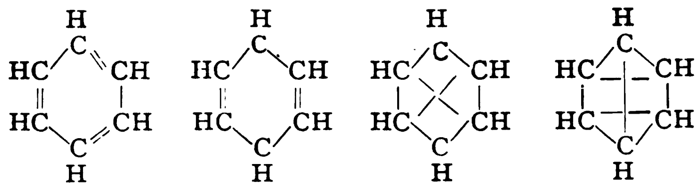


Fig. 16.

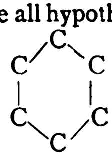
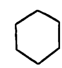
Diagram of Three Molecules of Acetylene united to form Benzene.

The six atoms of carbon in the benzene nucleus are represented as being linked in different ways according to the hypotheses of different chemists.

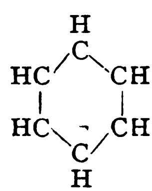
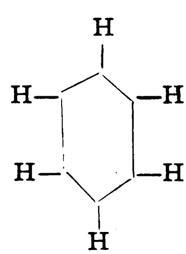
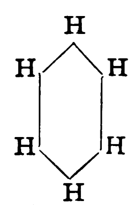
Thus benzene is represented by the following four graphic formulæ by the chemists whose names are placed under each :



Kekulé. Dewar. Claus. Ladenburg.

As these are all hypothetical, the benzene nucleus is often simply printed thus  or still more simply thus 

and benzene thus

 or thus  or thus 

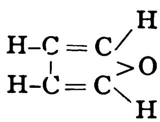
Intermediate Series.

Between the two great classes of carbon compounds which I have just mentioned, the fatty series, in which the compounds are linked so as to form an open chain, readily broken, and the aromatic series, in which the carbon atoms form a closed chain or ring which is difficult to break, a third or intermediate series may be placed.

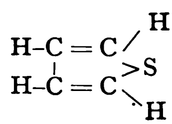
In this the carbon atoms form a close chain, but instead of this consisting of six carbon atoms closely linked together, as in the aromatic series, it contains only three or four carbons, either

linked to one another or having the chain completed by an atom of oxygen, sulphur, or nitrogen.

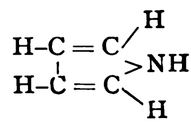
As examples of this series we have—



Furfuran.



Thiophene.



Pyrrol.

Three Classes of Carbon Compounds.

We have thus three great classes of carbon compounds :—

1st. The fatty or alcoholic class, with an open chain of carbon atoms.

2nd. The aromatic class, with a firm closed chain or ring containing six carbon atoms.

3rd. An intermediate class.

Elements and Radicals—Atoms and Molecules.

In their chemical relations these substances, acetylene, ethylene, methane, benzene, and furfuran, are practically *elements formed at a low temperature*, and may be fitly compared with the alkaline metals and those of the alkaline earths, which, if Lockyer's

Fig. 17.

Decomposition of Oxygen. **Formation of Ozone.**

Diagram to show the Decomposition of Oxygen and the Formation of Ozone by the Electric Spark. (After Lockyer.)

hypothesis be right, have been formed at enormously high temperatures. In describing this hypothesis I spoke of single atoms of elementary matter, or protyle, as Crookes calls it, as having been

existent at first, but under the conditions which now prevail single atoms (with few exceptions) seem incapable of independent existence. Atoms either join together with atoms of a like nature to form the molecule of an element, or with atoms of another element to form the molecule of a compound. When the molecule of an element is split up into single atoms, as, for example, the molecule of oxygen, by the electric spark, the single atoms do not remain apart, but immediately coalesce either with other single atoms to re-form a molecule of oxygen, or with two other atoms to form a molecule of ozone containing three atoms (fig. 17). Many elements seem to have but very slight chemical affinities for others when the atoms are already united to form a molecule, but when the molecule is split up, as for example during the process of chemical combination with other elements, the atoms have extremely active affinities just at the moment when they are set free, or, as it is termed, in their nascent condition. Thus nitrogen, which forms the bulk of our atmosphere, is an extremely inactive element in its ordinary condition, when all its atoms, as we believe, are united, two and two to form molecules. Yet, according to Armstrong,* this very inactivity probably depends upon the strength of its affinities, which hold the atoms together so strongly that they refuse to separate from each other and combine with other elements. But when the molecule is broken up and the atoms separate, the powerful affinities which impart to gunpowder, dynamite, or roburite their tremendous explosive powers become evident. Nitrogen in its molecular condition is the type of stability and inaction. Nitrogen in its atomic condition is the type of mobility and activity, and forms, along with carbon, the basis not only of our explosive compounds, but of organic life.

Physiological Action of Carbon and Nitrogen.

The properties of carbon and nitrogen compounds depend very greatly on the mode in which the atoms are combined, but if I were asked to describe in one word the general effect of carbon on the animal organism, I should say it is sedative, while that of nitrogen is exciting.

* Armstrong, *Journal of the Society of Chemical Industry*, July 30, 1887.

Radicals and Residues.

When the molecule of an element, such as hydrogen or oxygen, is broken up, it simply falls apart into two atoms which resemble each other, but when a substance containing more than one element is disintegrated it may not break up into the elements of which it is composed, but one or more atoms may, as it were, be knocked off, leaving a residual group of two or more atoms. This group behaves in much the same way as a single atom, and is, like it, incapable of independent existence. Such a group used to be called a *residue*, but the term *radical* is now given to it.

The Decomposition of Water.

Long ago water was regarded as an element. At length chemists succeeded in decomposing it, and thus they recognised it to be a compound. They then supposed it to be formed by the union of one atom of oxygen and one of hydrogen, and that during decomposition these simply fell apart and gaseous oxygen and hydrogen were formed.

But now that we regard water as a compound of two atoms of monovalent hydrogen and one of divalent oxygen* we see that the process of decomposition may be much more complicated.

When water (H_2O or H-O-H) is broken up it may not fall apart simply into oxygen and hydrogen, but one atom of hydrogen may be removed, leaving a single atom of hydrogen combined with one of oxygen. But the atom of oxygen being divalent (-O-) has only one of its affinities saturated by hydrogen, and the other remains free, so that the whole hydroxyl group (H-O-) acts like an atom with one free affinity, and is incapable of independent existence.

Hydroxyl.

This radical, hydroxyl (HO), is one of the most important in chemistry, and its presence in organic substances influences their physiological action to an enormous extent.

If the other atom of hydrogen were removed from hydroxyl

* The number of affinities in an atom is usually denoted by the term monovalent, divalent, trivalent, and so on, and this is indicated by Roman numerals placed above its symbol in a formula, thus: Na^{I}, O^{II}, N^{III}, or N^{V}, C^{IV}, etc.

we should have, instead of the radical (OH), the simple atom of oxygen $>O$ or $-O-$.

Amidogen, etc.

In the same way other compounds, such as ammonia, may have one or more of their atoms removed. When one atom of hydrogen is removed from ammonia (NH_3 or $H\text{-}N<^{H}_{H}$), it leaves the remaining group ($-N<^{H}_{H}$ or $-N=H_2$) with one free affinity, and the monovalent radical amidogen (NH_2) is formed. If two atoms of hydrogen are removed they leave the divalent group imidogen ($>N\text{-}H$ or NH^{II}), and if three are removed they leave the trivalent atom of nitrogen (N^{III}).

As, according to the view now usually accepted, no atom (with the exception of mercury and a few others) is capable of independent existence, it follows that if an atom of carbon is set free, it at once tends to unite either with another atom to form a carbon molecule, or else with other elements to form a carbon compound.

RECENT VIEWS OF CHEMICAL ACTION.

The fact that the hypothesis usually held at present regarding the chemical affinities of atoms and molecules is not of universal application, but finds an exception in the case of mercury and some other elements, appears to indicate that something more is

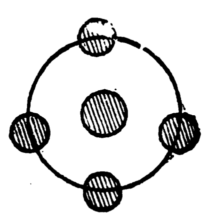


Fig. 18.
Diagram of Methane (CH_4). After Mendeleeff.

required. Indeed, the idea of affinities which we now hold is simply to be regarded as a very useful working hypothesis, which

enables us to class together chemical phenomena already known, and even to predict new facts, in the same way as the Ptolemaic theory of the movements of the planets in cycles and epi-cycles enabled men to predict eclipses. But just as that cumbrous theory has now been completely swept away, so it seems probable that our present cumbrous ideas of chemical affinity may also give way to simpler views. Mendeleeff, who with prophetic insight has not only predicted the existence of new elements, but described their properties correctly while they were still practically unknown, has, in a recent lecture, expressed his views that chemical affinities will shortly be brought under Newton's third law of motion. According to this idea chemical compounds and solar systems are built upon the same plan, and methane, consisting of a carbon and four hydrogens, might be compared to Jupiter and his four moons. Fig. 18.

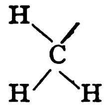
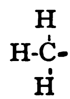
Substitution in Carbon Compounds.

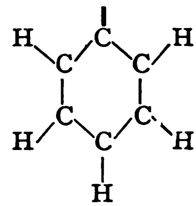
By treatment of the carbon compounds belonging either to the fatty or the aromatic series it is found that one or more atoms in the molecule may be replaced by others. Thus one atom of hydrogen in methane $\left(\begin{smallmatrix}H\\H\end{smallmatrix} > C < \begin{smallmatrix}H\\H\end{smallmatrix}\right)$ may be removed and replaced by chlorine, iodine, or bromine, forming chloro-methane $\left(\begin{smallmatrix}H\\H\end{smallmatrix} > C < \begin{smallmatrix}Cl\\H\end{smallmatrix}\right)$, bromo-methane $\left(\begin{smallmatrix}H\\H\end{smallmatrix} > C < \begin{smallmatrix}Br\\H\end{smallmatrix}\right)$, or iodo-methane $\left(\begin{smallmatrix}H\\H\end{smallmatrix} > C < \begin{smallmatrix}I\\H\end{smallmatrix}\right)$.

These in their turn may be replaced by hydroxyl, forming methylic alcohol $\left(\begin{smallmatrix}H\\H\end{smallmatrix} > C < \begin{smallmatrix}O\text{-}H\\H\end{smallmatrix}\right)$.

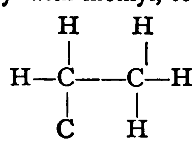
Radicals; their Classification and Combinations.

In all these changes the group CH_3 or $\left(\begin{smallmatrix}H\\H\end{smallmatrix} > C <_{H}\right)$ has remained intact, and has played the same part in the compound that an atom of potassium or sodium would have done in similar circumstances. This group, which has thus acted as the basis or root of the compound, has therefore been called a radical.

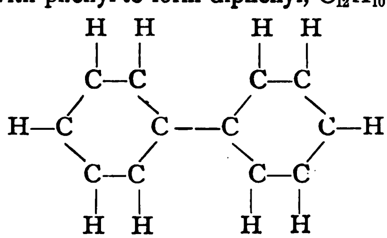
Classification.—Such radicals may belong either to the fatty series, like methyl, CH_3 or  or 

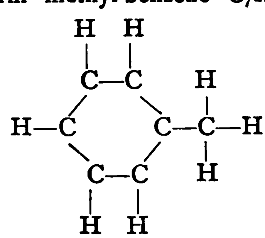
or to the aromatic series, like phenyl C_6H_5, 

Combination.—They may unite either with other radicals of the *same series*, as—methyl with methyl, to form ethane C_2H_6,

 (ethane)

or phenyl with phenyl to form diphenyl, $C_{12}H_{10}$



Or they may unite with radicals belonging to *another series*, as methyl with phenyl to form methyl-benzene C_7H_8, or, as it is usually called, toluene, 

Links.—But instead of two such radicals becoming directly united, the bond of union may consist either of a carbon atom alone ($>C<$), or of a carbon atom with one or two atoms of hydrogen attached to it $\left(-\overset{H}{\underset{H}{C}}-\right)$; or the uniting link may consist of

oxygen ($-O-$), of sulphur, nitrogen, phosphorus, arsenic, antimony, boron, silicon, and indeed, probably, of any element the atom of which has at least two affinities, so that it is able to connect two radicals.

NITROGEN COMPOUNDS.

Nitrogen, like carbon, seems to have the power of uniting with itself by either one or two bonds, so that it is able to form different compounds according to the mode in which its atoms are connected. Thus, when the two atoms of nitrogen are connected singly, and the remaining two affinities of one are saturated with hydrogen, and those of the other with hydrogen and an organic radical, or with two organic radicals, we obtain a class of compounds known as hydrazines; but when the atoms are linked to one another by two affinities they form azo and di-azo compounds:

$\genfrac{}{}{0pt}{}{H}{H}{>}N{-}N{<}\genfrac{}{}{0pt}{}{CH_3}{H}$	$C_6H_5{-}N{=}N{-}C_6H_5$	$C_6H_5{-}N{=}NCl$
Methyl Hydrazine.	Azobenzene.	Diazobenzene Chloride.

Nitriles and Iso-nitriles or Carbylamines.

Nitrogen is peculiar in another respect, viz., that sometimes it appears to have only three affinities, while at another it has five (*vide* p. 23 and fig. 12). When it becomes connected with carbon in its triatomic condition it saturates three affinities of the carbon, leaving one free ($-C{\equiv}N$), and compounds of this description are called nitriles. On the other hand, when nitrogen is pentavalent and becomes united with carbon the four affinities of the latter element saturate four of nitrogen, leaving one affinity of nitrogen free ($-N{\equiv}C$). In both cases the free affinity may unite with hydrogen or with a radical.

It is thus evident that we may have two substances having exactly the same chemical composition, RCN and RNC, but with this difference, that R, which may stand for an organic radical, is connected in one case with an atom of nitrogen ($R{-}N{=}C$), and in the other with an atom of carbon ($R{-}C{\equiv}N$). It might be considered that this difference is of no importance, and that the two

bodies would be practically identical, but this is by no means the case. On the contrary, their physiological action is very different.

Those bodies (nitriles) in which the nitrogen is trivalent, and the radical is united to carbon, are comparatively inactive, whereas those in which it is united to nitrogen are very poisonous. This difference in the arrangement of the atoms is usually known as chemical constitution, as distinguished from chemical composition, by which we mean the number and kind of atoms of which the substance is composed.

Chemical Composition, Chemical Constitution, and Chemical Structure.

I had intended at first to call the subject of my lectures "The Relation between Chemical Constitution and Physiological Action," but I found that this title would not include the whole subject which I wished to discuss. For I wished to include the alteration which may be brought about in the physiological action of a substance by the simple multiplication of its parts without altering their arrangement, as, for example, the difference between the action of one of the lower alcohols, ethylic alcohol; and one of the higher, amylic alcohol. These two alcohols are built on exactly the same type, and the relation of the parts is similar, but the number of parts is greater in amylic than ethylic. I therefore resolved to change the title of the lectures to "The Relation between Chemical Structure and Physiological Action," as the word "Structure," I think, may be fairly made to include the number of component atoms in the substances, as well as their relation to one another.

Chemical Constitution.

To make the subject of chemical constitution clearer, I may perhaps be allowed to make use of a very homely simile.

I have here a pocket-knife with a number of blades. At present these blades are all shut, and the knife may be given to a child to play with or carried in the pocket without the least danger. If I open one of the blades, however, the case is very different. The composition of the knife is exactly the same as

before, but by altering the relation of the parts to one another I have converted a harmless plaything into a dangerous weapon. In the case that I have just referred to, of the compound of nitrogen and carbon, an alteration in the relation of its parts has a similar effect to the opening of the knife, and converts the comparatively harmless nitrile into the deadly carbylamine. Again, while I keep the same handle to my knife, I may alter its uses by opening out a book-hook, a gimlet, or a file, and in a similar way we may alter the functions of an organic radical which we may compare to the haft of the knife, by attaching to it an atom of amidogen, chlorine, or hydroxyl. If I wish to cut through a piece of cord, or something else out of my reach, with my pocket-knife, I may effect my purpose by tying my knife to a piece of stick, and if that should not be long enough, attaching another and yet another piece, until I have got my handle sufficiently long for my purpose. Such a process as this may be compared to adding on carbon atom to carbon atom in a lengthening chain in the higher paraffins, but just as my shank would by-and-by become too heavy and cumbrous to allow me to handle it, and thus becomes useless for my purpose, so we find that the higher paraffins, although from their high molecular weight they ought to be powerful anæsthetics, are too sparingly absorbed to have any physiological action at all, and instead of producing either intoxication or anæsthesia like marsh gas, are simply used, under the name of vaseline, to protect the skin.

Formulæ.

In discussing chemical questions we are accustomed to use two sorts of formulæ—the graphic, in which we represent diagramatically the relative position of the atoms in a compound, and the ordinary, in which we write down its nature in symbols. In trying to convey to you an idea of chemical constitution I have used one illustration which might be compared to a graphic formula, and in order to make the matter clearer I may, perhaps, be allowed to use another which is more analogous to an ordinary formula. In writing down chemical formulæ we use certain

letters to denote the elements, generally the initial ones of their Latin names, and the number and position of those convey to a chemist, in a certain degree, an idea of the composition of the substance represented by them. With a comparatively small number of letters of the alphabet we are able to form a great number of words and to represent a great number of ideas, and with a small number of elements we can form many compounds. Slight alterations in the composition of words, the introduction or abstraction of a single letter, will often completely change their meaning, and slight alterations in chemical substances will change their properties.

Modification by Altering Composition—Omission.

Thus one often sees in railway carriages the announcement to passengers, "WAIT UNTIL THE TRAIN STOPS," modified by some one scraping out the T, so that it reads, "WAIT UNTIL THE RAIN STOPS," and then some one else scrapes out the lower part of the letter R, after which it reads, "WAIT UNTIL THE PAIN STOPS."

I frequently see an example which is indeed, I think, a common one both in schools and colleges. On a certain door the words "CLASS ROOM" were originally painted, but certain ingenious students have amused themselves by obliterating first the C and then the L, and turning the original words first into "LASS ROOM," and then into "ASS ROOM." Just as the successive removal of those two letters completely altered the meaning of the original word, so the removal of the letters symbolic of two elements from a chemical formula will completely alter the nature of the substance represented by it.

In both the instances which I have just given the alterations have been effected in the composition of the words by removal of the constituent letters, but the relation of the remaining ones to one another has not been altered.

Modification by Alteration of Composition—Addition.

We are frequently able to make additions to a word which somewhat modify its sense without, however, altering its meaning

in any essential particular. The root or radical remains the same, and the omissions only modify it. Thus we may say class-room, dining-room, drawing-room, bedroom, or we may say roomlike, roomy, roomful; but in all these words we have the idea of a room as the essential meaning.

Modification by Altering Relation of Parts or Constitution.

By altering the arrangement of the letters, however, we produce a completely different effect, and instead of ROOM we get MOOR. By this slight alteration we convert a word suggestive of comfort, enclosure, warmth, and society into one suggesting expanse, exposure, cold, and desolation, a change which is paralleled by the example I have already mentioned of RCN. and RNC. The word moor may also be modified in much the same way as the word room. Such modifications as I have spoken of usually affect the significance but slightly, yet occasionally a slight addition may alter the sense of the word as completely as a difference in its structure. Thus, Moorish, instead of conveying a sense of bleakness and coldness, brings before the mind ideas of Oriental grandeur, sunshine, and activity. The reason here of course is that the root moor, in the two words moorland and Moorish, although alike in appearance and sound, is really quite different.

Effect of Alterations in Chemical Structure on Physiological Action.

But in studying the physiological action of various chemical substances we find that while usually certain alterations or additions only modify the action of the radical to a slight extent, yet now and again we meet with quite unexpected cases where slight modifications produce an altogether unexpected effect. Thus, sodium acetate has got a very slight physiological action indeed, but when one atom of hydrogen in the acetic acid is replaced by bromine the result is mono-bromo-acetate of soda, which has a most remarkable action upon the muscles of the frog, rendering them so rigid that the animal becomes like a piece of wood. Another curious example is afforded by phenol and aniline, both of which are markedly poisonous, but ortho-amido-

phenol is innocuous. Another example possesses a special interest from the possible bearing it may have in the causation of uræmic poisoning. This will be discussed later on, but the substance in question is oxalethylin, which has an action like atropine on the brain, pupil, and vagus, stimulating the brain, dilating the pupil, and paralysing the inhibitory powers of the vagus. But if one atom of hydrogen in it be replaced by chlorine the resulting body, chloroxalethylin, while still retaining its power over the vagus, no longer dilates the pupil, and acts as a soporific to the brain like morphine.

METHODS OF TREATING THE SUBJECT OF THE LECTURES.

The relation between chemical structure and physiological action is a subject which might be treated either from a chemical or from a physiological point of view. Each plan would possess certain advantages and certain disadvantages.

A complete treatment of the subject would be easier from the chemical side, and such a method might also be more convenient for reference; but the main object of these lectures is to deal with the subject in relation to the prevention, control, and cure of disease, and the physiological method is, I think, better adapted for this purpose.

I, therefore, propose to consider the causes of disease and the functions of the organism, and to discuss the manner in which these are affected by alteration in the chemical structure of the remedies we employ.

NATURE OF DISEASES—MICROBES AND POISONS.

We may regard disease as such an alteration in the body as either causes a want of ease in the patient at the time or will cause it if its action is not arrested.

As I have already said in speaking of the progress of pathology, disease was formerly looked upon as something apart from the patient, but now we regard the patient and the disease as living in the same way and influenced by similar conditions.

Poisons Produced by Microbes.

For a good while the microbes were looked upon as directly

causing disease by affecting the tissues of the patient; but now, since chemical investigation has been applied to the processes of disease and the products of putrefaction and fermentation, we are beginning to look upon many of the symptoms which occur in consequence of the action of microbes as being due not to their direct action upon the tissues, but to their indirect action in forming poisons; to regard, in fact, the symptoms they produce as bearing a similar relation to the microbes as the symptoms of intoxication do to the yeast plant. Yeast does not produce intoxication. It is the alcoholic products of its action upon saccharine fluids which make a man drunk. Similarly, the symptoms in cases of infective disease are probably due to poisons produced by microbes rather than to the microbes themselves.

Panum's Researches.

In 1856 Panum demonstrated that the poison which occurs in putrefying meat is a chemical substance and not a living organism, although it may be formed by organisms, for he was able to boil it for eleven hours, and then to dry it completely at boiling heat, without destroying its poisonous properties. He showed that the symptoms produced by the putrid poison were different from those produced by various ammoniacal salts, leucine and tyrosine, which he administered to the animals for the purpose of comparison. He was uncertain whether the poison acted like an alkaloid, such as strychnine, directly upon the nervous system, or whether it acted upon the blood, causing decomposition in it, and leading to the production of substances which poison the nerve-centres. At all events he felt sure that it did not act like an ordinary ferment, such as pepsin or ptyalin, for it was not destroyed like them by prolonged boiling.

Selmi's Researches—Ptomaines.

In 1870 Selmi brought prominently forward the chemical nature of the poisonous products which resulted from the decomposition of albuminous matters by microbes. He concluded that their actions might resemble those of the vegetable alkaloids, but he did not separate or identify any individual substance, although he gave the whole class the name of ptomaines.

Cholera and Muscarin Poisoning.

In 1873 I read a paper before the British Association at Bradford,* in which I pointed out the striking resemblance which exists between the symptoms of cholera and those of poisoning by muscarine, and I suggested atropine as a possible remedy in cases of cholera, on account of its remarkable power to antagonise muscarine. I came to no conclusion regarding the exact nature of the cholera poison, nor did I distinguish between microbes or actual alkaloids which might be present in it.

Bacteriology and Chemistry.

Since that time the researches of Koch and the methods he has introduced have given an enormous impetus to the study of bacteriology, while the isolation by Nencki of a definite ptomaine and the discovery of many more by Brieger have put the chemistry of putrefaction on an entirely new basis.

The Relation of Microbes to Disease.

In discussing the relation of microbes to disease we may consider—

1st. The microbes themselves *outside the body*, and the poisons they may produce;

2nd. The microbes themselves, and the poisons they may form *in the intestinal canal;* and—

3rd. The action of microbes or their products when actually circulating *in the blood or* present in the *tissues.*

It is, of course, a question not only of great theoretical interest, but one likely to be of great practical importance, Do the microbes break up the albuminous substances or carbohydrates which they attack by means of their actual protoplasmic structure? or do they, like the higher animals, secrete organic ferments or enzymes, by means of which the disintegration is actually carried on?

* Abstract in British Association Reports for 1873. Paper reprinted in the author's "Disorders of Digestion," p. 262 (London: Macmillan and Co.).

Mode in which Microbes attack Protoplasm.

It is evident that if the decomposition of albumen, starch, or fat, for example, be due to the actual protoplasm of the living microbes, it will at once cease if these microbes be killed. But if it be dependent on a ferment which is secreted by the microbes it may continue, to a certain though limited extent, after they have been destroyed, just as the pepsin which is secreted by the stomach of a pig may carry on digestion after the pig itself has been killed.

This question was investigated by Kühne in 1877. He came to the conclusion that the fermentative action of bacteria was not the same as that of the pancreas, and he did not succeed in isolating any ferment by extracting bacteria with water or glycerine, as he would have done on treating a pancreas.

Formation of Enzymes by Microbes.

The probability that microbes formed ferments seemed so great, however, that I thought it worth while to take up the question again. The difficulty of such a research, and the time required to make the necessary experiments, completely prevented me from attempting to do it alone; but I have been so fortunate as to secure the co-operation of Dr. Allan Macfadyen, whose skill in experimenting has enabled us to get some positive and interesting results.*

* "The Ferment Action of Bacteria." Proceedings of the Royal Society, vol. xlvi., p. 542. By T. Lauder Brunton, M.D., F.R.S. and A. Macfadyen, M.A., B.Sc. Received March 23, 1889. The chief objects which we proposed to ourselves in this research were:—

(*a*) To discover whether microbes act on the soil upon which they grow by means of a ferment.

(*b*) Whether such a ferment can be isolated, and its action demonstrated on albuminoid gelatine and carbohydrates, apart from the microbes which produce it, in the same way that the ferments of the stomach and pancreas can be obtained apart from the cells by which they were originally secreted.

The results of our inquiry were briefly as follows:—

(1) The bacteria which liquefy gelatine do so by means of an enzyme.

(2) This enzyme can be isolated, and its peptonising action demonstrated, apart from the microbes which produce it.

The object of the inquiry was to ascertain whether microbes act upon the soil upon which they grow by means of a ferment, and whether such a ferment can be isolated and its action shown apart from the microbes which produce it, in the same way that the ferments of the stomach and pancreas can be separated from the cells by which they are originally secreted. The results of the inquiry were that bacteria liquefy gelatine by means of an enzyme which can be isolated and which will continue to act after the microbes have been destroyed. Like the ferments of the pancreas, this enzyme acts most readily in alkaline solutions. Bacteria seem to have the power of adapting themselves to the soil on which they grow, and of manufacturing a ferment suitable to their needs, for the same bacilli when grown in starch paste, instead of on gelatine or in beef tea, produced a different ferment, which would convert starch into sugar, but would not act upon gelatine.*

The difficulty of such investigations is so great that however carefully the experiments may have been made, there is always a natural hesitation to accept the results of any observers till they have been confirmed by others. At the same time I believe that our results are substantially correct.

After we had been occupied with this research for several months we learned that similar results had been obtained by Bitter, who has found that Koch's cholera bacillus produces in

(3) The most active enzyme is that formed in meat broth.

(4) Acidity hinders, alkalinity favours its action.

(5) The bacteria which form a peptonising enzyme on proteid soil can also produce a diastatic enzyme on carbohydrate soil.

(6) The diastatic enzyme is not so readily separated from the microbes which produce it, but where that has been accomplished its action on starch can still be demonstrated.

(7) The diastatic enzyme has no effect on gelatine, and *vice versa*.

(8) The bacteria are capable of evincing an adaptiveness to the soil in which they grow.

(9) The microbes are capable of digesting other similar bodies, such as dextrose and muscle.

(10) Fatty matter was not affected.

* Brunton and Macfadyen, Roy. Soc. Proc. vol. xlvi.

meat peptone a peptonising ferment which is quite distinct from the bacillus itself, and continues active after the bacillus itself is destroyed, and similar results have also been obtained by Sternberg. This ferment resembled pancreatin rather than pepsin, by acting more vigorously in alkaline than in acid solutions. We have not seen the original work of Bitter or Sternberg, and know it only from a brief abstract.*

One point that comes out in the experiments of Dr. Macfadyen and myself is that the microbes themselves may be destroyed by a temperature which does not destroy the activity of the ferment which they have formed.

Relation of the Ferments formed by Microbes to Poisoning by Meat.

The practical application of these results in regard to the prevention of disease is that they seem to show that meat which has become tainted by the presence of putrefactive microbes may possibly be cooked sufficiently to destroy the microbes themselves, while the ferments they have formed continue to decompose the meat and give rise to poisonous substances. We can thus see how a cold beef-steak pie or other cold meat may become poisonous and produce serious symptoms, although the same food may have been eaten with impunity immediately after being cooked, because during the process of cooking and standing afterwards poisons may have been formed in the meat, although there were none in it immediately after it had been removed from the oven, and any microbes present were likely to have been killed by the cooking. The frequency with which meat very slightly tainted must be eaten in summer, and the common rule of not eating game at all until it is somewhat "high," as it is termed, make one rather wonder why poisoning by ptomaines formed in such meat and game does not occur more frequently, although I believe that it occurs, in a slight degree, more frequently than people are generally willing to allow.

* "Ptomaines and Leucomaines," by Victor C. Vaughan and Frederick G. Novy, 1888, p. 96 (Philadelphia: Lea Bros. and Co.).

LECTURE II.

PREVENTION OF DISEASE—(*continued*).

EXPLANATION OF THE DANGER OF DISEASED MEAT.

SOME very interesting experiments by Bocklisch may perhaps explain this rarity of ptomaine poisoning. In experimenting with pure cultivations of the vibrio proteus, better known as "Finkler's bacillus," he found that it did not seem to produce any poisonous substances, although it occurs in the dejecta of patients who have been suffering from sporadic cholera, and is supposed to cause the disease. It occurred to him, however, that it is never present in the human intestine as a pure cultivation, and that possibly the presence of another bacillus along with it might cause the formation of the poisonous products in sporadic cholera. He therefore mixed some other putrefactive bacteria with it, and found that the mixed bacilli formed a highly poisonous substance, methylguanidine.

In the same way it seemed not unlikely that cases of acute poisoning by meat or game may be due to the accidental presence of more than one kind of bacillus, leading to the formation of specially poisonous products. More especially is this likely to be the case if one of them is a pathogenic microbe which has already produced disease in the beast or bird yielding the meat, and a certain amount of decomposition of its tissues before its death.

IMPORTANCE OF FERMENTS AND PRODUCTS OF ALBUMINOUS FERMENTATION IN RELATION TO POISONING AND DISEASES.

Decomposition of Albumen.

Albuminous substances are of a very complex composition, and contain a huge number of atoms. In the process of decomposition by heat (as in burning or dry distillation), by putrefaction, or

by the action of enzymes (such as pepsin or trypsin), the large molecule of albumen becomes decomposed, yielding simpler and simpler substances. The huge albuminous molecule will not diffuse through vegetable parchment. The final products of its decomposition, such as compound ammonias and organic acids, diffuse readily. Between these two stages we find intermediate substances—albumoses and peptones.

Albumoses and Peptones.

Albumoses and peptones are amongst the products of normal digestion, but they are now acquiring a special interest from the discovery that, when introduced into the blood without passing through the liver, these digestive products may act as powerful poisons.

Albuminous Substances as Food and Poison.

It seems strange that food and poison should be so nearly allied, and that, while albuminous substances are indispensable for the maintenance of life, the substances into which they must be broken up before they can be assimilated will kill an animal if they are applied in a wrong way and are injected into the jugular vein instead of being absorbed from the intestine and passing through the liver. A house is very necessary for people to live in, and if it has to be transferred from one place to another it may be occasionally, as in Chicago, mounted on rollers and moved on; but in this country we generally pull it down and rebuild it. In this process, as Hermann has well put it, we separate the bricks from one another, and then put them together again. The bricks are quite harmless, and are very useful when properly applied to building the house, but a brick may be a fatal weapon if it is misapplied by being flung at a man's head. The albumoses and peptones into which albumins split up in the process of digestion are much more readily absorbed than the albumins themselves would be, and when they are put together again in the proper way in the portal vein or liver they support the strength, maintain life, and do no harm, but only good, to the organism.

Poisonous Albumins—Fibrinogen.

Most of us, no doubt, have eaten and enjoyed sweetbreads, which sometimes consist of the pancreas and sometimes of the thymus gland of the ox, and have received nothing but pleasure and strength from doing so; but it has been shown by the gifted young physiologist and pathologist whose recent untimely death has been such a blow not only to his friends, but to scientific men throughout the world, Dr. Wooldridge, that the juice of the thymus gland, if injected into the veins of a rabbit, will cause almost instantaneous clotting of the blood throughout the body, so that a small quantity of this albuminous juice, containing a kind of fibrinogen, kills the animal as quickly as a toxic dose of hydrocyanic acid, or a bullet through its head.

Poisonous Digestive Products—Albumoses and Peptones.

The albumoses and peptones formed during digestion seem to have just the opposite action. They prevent coagulation altogether, and produce coma, convulsions, and death.

Serpent Venom—Jequirity.

Moreover, the venom of serpents has been shown by Weir Mitchell, Reichert, and others to belong, in part at least, to this class of substances, and some vegetable poisons do so also, for in a most interesting research Martin has shown the jequirity poison also to be an albumose. The poisonous action of albumoses is destroyed by boiling, and as the venom of the cobra is weakened but not completely destroyed by boiling, it is probable that it does not consist entirely of an albumose, but contains some other poisonous substance as well.

Diphtheritic Poison.

The interesting point in the relation of ferments or albumoses to disease is that the poisons formed by some disease-germs belong to this class. Thus Roux and Yersin have found that the poison of diphtheria has its virulence completely destroyed by boiling, just in the same way as the poison of the jequirity seed.

Products of more complete Decomposition of Albumin, Alkaloids, Ammonia.

But as albuminous molecules become more broken up, the products of their decomposition no longer have their poisonous properties destroyed by heat. I may perhaps again be allowed to use a simile which I have employed on a former occasion,* and liken the food we eat to the utensils which we use. A plate or a tumbler, although it might, like the brick, occasionally be awkward if used as a missile, can hardly be called dangerous; but when broken or splintered the fragments may cut or pierce, and inflict serious or even fatal injuries. If the fragments are large they can easily be cemented into a whole utensil, and thus be deprived of their injurious character. In like manner albumoses and peptones are built up into non-poisonous albuminous substances in the liver and portal vein. If the splinters are smaller it will be difficult or impossible to do this; and the ptomaines or alkaloidal substances resulting from the further decomposition of albumin may not undergo synthesis in the portal system, but pass through the liver, and act as poisons in the general circulation. But if we break these splinters by pounding them into fine dust, we may again make them almost completely harmless, and in the same way the final products of albuminous decomposition, ammonia and carbonic acid, have but a very slight poisonous action, and only kill when used in very large quantities, while the ptomaines, which may be likened to the splinters, are very deadly.

Ptomaines and Leucomaines.

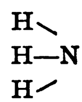
The alkaloids formed by the decomposition of albumin in the dead body are termed "ptomaines," while those which are formed in the living body have received from their discoverer, A. Gautier, the name of "leucomaines."

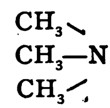
NATURE OF PTOMAINES. POISONOUS AMINES OR TOXINES.

The chemical constitution of all the ptomaines has not been ascertained, but a number of them seem to be compound ammonias or amines. If one happens to be passing through a fishing

* "Disorders of Digestion," p. 277 (London: Macmillan and Co.).

village at certain times of the year, one may notice a peculiarly pungent, disagreeable smell from herring barrels. This smell is due to trimethylamine, a substance which some years ago was recommended as a cure for rheumatism. It consists chemically of ammonia, in which 3 atoms of hydrogen have been replaced by 3 of methyl; thus:


Ammonia.


Trimethylamine.

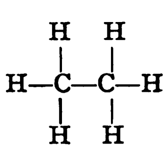
This substance is one of the products of decomposition of albuminous substances, and has been found by Brieger in rotten cheese, and also in the cadaver.

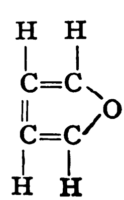
A similar substance, dimethylamine, in which only 2 atoms of hydrogen are replaced, is found in decomposing glue; but these substances, though poisonous to frogs, have little toxic power in mammals, and are of little importance in connection with poisoning.

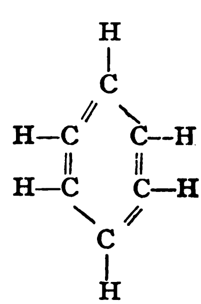
Chemical Structure of Alkaloids.

In speaking of carbon compounds I mentioned that they form three classes: (1) the alcoholic or fatty, in which the atoms are arranged in an open chain; (2) the aromatic, in which the atoms form a closed chain or nucleus; and (3) an intermediate class.

As examples of these we have:

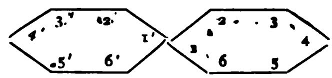

Ethane
C_2H_6


Furfuran.


Benzene.

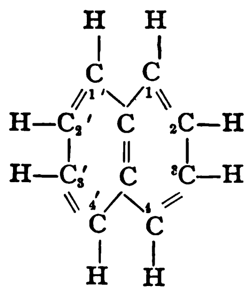
I should mention that benzene nuclei seem to unite with each

other either by one or more affinities. When they unite by one diphenyl is formed.



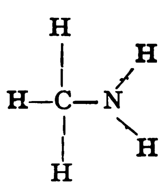
Diphenyl.

When they unite by two naphthaline is formed, thus:

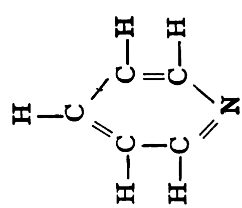


These substances have all more or less basic properties and unite with acid radicals.

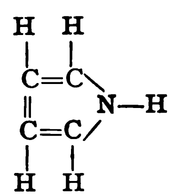
Nitrogen may combine with bodies of all three series, and give rise to a series of nitrogenous bases, thus:



Methylamine.

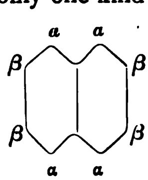


Pyridine.



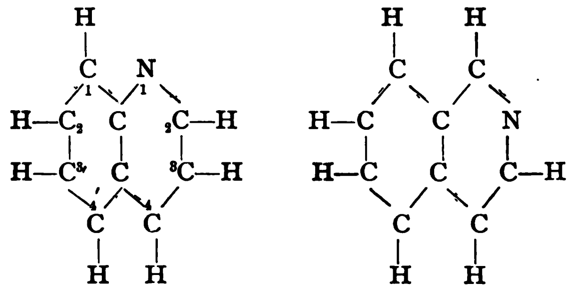
Pyrrol.

As the benzene nucleus is symmetrical, the product is the same whichever carbon atom is replaced by nitrogen, so that we have only one kind of pyridine. But this is not the case with chinoline,



for in it we have four carbon atoms, having a position similar to each other (α), but differing from that of four others (β), which also resemble each other. We have thus two chinolines—chinoline and iso-chinoline, and the latter is very important,

as it seems to form the basis of some of the most important alkaloids.



Chinoline or Quinoline.	Iso chinoline or Iso-quinoline.

It will be noticed that each of the bodies just mentioned may be regarded as ammonia from which hydrogen has more or less completely been displaced, and the affinities of the nitrogen have been saturated by other atoms or groups.

Amines—Amides.

The substances formed by the substitution of alkyls for hydrogen in ammonia are termed amines, and those formed by substitution of an acid radical are called amides. If 1 atom of hydrogen is replaced by an alkyl, *e.g.*, methyl CH_3, the resulting body is called a primary, if 2 a secondary, and if 3 a tertiary amine, thus:—

$H-\overset{\displaystyle H}{\overset{\vert}{N}}-H$	$H-\overset{\displaystyle CH_3}{\overset{\vert}{N}}-H$	$CH_3-\overset{\displaystyle CH_3}{\overset{\vert}{N}}-H$	$CH_3-\overset{\displaystyle CH_3}{\overset{\vert}{N}}-CH_3$
Ammonia	Methylamine	Dimethylamine	Trimethylamine
	(1ary amine)	(2ary amine)	(3ary amine)

In the examples of amines just given the nitrogen is not connected by more than one affinity to any single carbon atom, but it may be linked by either one, two, or three affinities to a single carbon atom. Thus, in pyrrol two atoms of hydrogen have been substituted, and it is therefore a secondary amine, but instead of the two affinities of nitrogen set free by the removal of hydrogen having been saturated by two atoms of carbon, as in dimethylamine, they are saturated by one. Pyridine may be regarded as ammonia in which all three atoms of hydrogen have been substi-

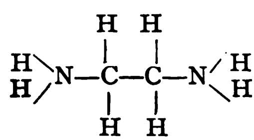
tuted, and it is therefore a tertiary amine, but all three affinities of the nitrogen are saturated by two carbon atoms.

Nitriles.

When all three atoms of hydrogen in ammonia are replaced by a single atom of carbon in a substance it is called a nitrile. As only one affinity of the carbon atom then remains free it cannot enter into a closed ring, but can only form part of an open chain, and therefore the nitriles all belong to the fatty series.

Monamines—Diamines—Triamines.

When an amine is formed from a single ammonia group it is termed a monamine. But amines may be formed by substitution, occurring in 2, 3, or 4 ammonia groups held together by atoms or radicals having more than one affinity, and the resulting bodies are termed Diamines, Triamines, and Tetramines respectively.* Thus—



Ethylene Diamine.

Alkaloids—Amines—Amides—Toxines.

The term alkaloid is usually applied to all compound ammonias derived from plants and animals. But it is evident from what I have already said that in some of these ammonias, like trimethylamine, the nitrogen may be connected only with carbon groups belonging to the fatty series, while in others, like pyridine or chinoline, it may be, so to speak, built into the aromatic carbon ring.

In order to distinguish between these two divisions, some chemists now restrict the term alkaloid to substances of the pyridine or chinoline series, while the term amines is retained for the other products of substituting hydrogen in ammonia by alkyls. As a short name for poisonous amines, such as choline neurine, and muscarine, the word "toxines" has been proposed.

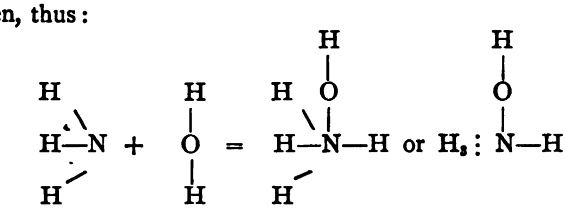
* *Vide* "Beilstein, Organische Chemie," vol. i., pp. 398-400, Leipzig, 1881.

Ammonia and Ammonium.

I have already mentioned that nitrogen, although generally trivalent, is sometimes pentavalent, and while we write NH_3 as the formula of ammoniacal gas, the formula of ammonium chloride is NH_4Cl.

The hydrochloric acid, HCl, attaches itself directly to the ammonia or to the compound ammonias in which hydrogen has been replaced by radicals. In the case of the ammonia itself, we assume that a hypothetical substance, ammonium (NH_4), has been formed which behaves like the alkaline metals potassium and sodium. Consequently we term the compound thus formed ammonium chloride, as it corresponds to sodium chloride; but where we do not know the nature of the compound ammonia as in some of the organic alkaloids like morphine, we term the compound a hydrochlorate, *e.g.*, we say hydrochlorate of morphine or morphia (corresponding to ammonia), instead of saying chloride ot morphium.

It is generally believed that a similar change from trivalent to pentavalent nitrogen occurs when ammoniacal gas is dissolved in water. It then combines with the water, the latter splitting up, and one atom of hydrogen combining directly with the nitrogen, while the remaining OH becomes attached by its oxygen to the nitrogen, thus:



Ammonia gas. Water. Ammonium hydroxide. (Liquor ammoniæ.)

Some of the most important ptomaines are built on this latter type, namely, that of ammonium hydroxide. In them the 4 atoms of H are replaced by radicals, but they retain the hydroxyl (OH).

When all four atoms of hydrogen in ammonium hydroxide are

displaced by monovalent alcohol radicals (alkyls) we obtain ammonium bases, *e.g.*, tetramethyl ammonium hydroxide. By the addition of an acid, *e.g.*, hydrochloric acid, the hydroxyl may be replaced by an acid radical, and a salt of the base obtained, *e.g.*,

H | O Me╲ | Me—N—Me Me╱	Cl H╲ | H—N—H H╱	Cl Me╲ | Me—N—Me Me╱
Tetramethyl ammonium hydroxide.	Ammonium chloride.	Tetramethyl ammonium chloride.

Physiological Action of Amines and Compound Ammoniums.

When we pass from an amine in which the three affinities of triad nitrogen are combined with three alkyl groups to a compound ammonium in which four affinities of pentad nitrogen are combined with four alkyl groups and the fifth with hydroxyl or with an acid radical, we notice a great change occur in the physiological action, both in regard to extent and kind. For the compounds containing pentad nitrogen are not only much more poisonous, but they have a marked tendency to a convulsant action, which is much less or is completely absent in those containing triad nitrogen.

Hydramines or Oxyethyl Bases.

In the amines and ammonium bases H is replaced by *monovalent* radicals (alkyls), and as each of these has only the one affinity by which it becomes attached to the N, none of them can take on an additional hydroxyl, and consequently the only hydroxyl in the amine or ammonium base is the one directly connected with N.

But this is not the case when a *divalent* alcoholic radical (alkylen) replaces H in ammonia or ammonium hydroxide, for the hydroxyl may then be connected to the alkylen only, or there may be two hydroxyl groups, one of which is connected to the alkylen and the other to the nitrogen.

* Brunton and Cash, *Phil. Trans.*, part I., 1884, p. 219.

$$\begin{array}{l} H{-}O{-}CH_2.CH_2\diagdown \\ \qquad\qquad\qquad\; H{-}N \\ \qquad\qquad\qquad\; H\diagup \end{array}$$

Ethylene hydramine.

$$\begin{array}{l} \quad\; Cl \\ H\diagdown | \\ H{-}N{-}CH_2.CH_2.OH \\ H\diagup \end{array}$$

Ethylene hydrate ammonic chloride.

As the alkylen in these last examples has a hydroxyl attached to it, an abbreviation of this word is introduced into their names, and they are termed *hydroxy*ethyline or more shortly *oxy*ethyl bases or *hydr*amines.

Formation of Ptomaines.

A glance at the accompanying table will show that three of the commonest (namely, neurine, choline, and muscarine) may be formed from trimethylamine and alkylen radicals, in the same way as caustic ammonia is formed from ammoniacal gas and water,* viz., by the hydroxyl group passing from the alkylen to the nitrogen of the trimethylamine, while the residue also becomes attached to the nitrogen.

Ammonium hydroxide $\begin{array}{l} (O{-}H)< \\ \qquad | \\ H_3 : N{-}(H)< \end{array}$ formed from $H_3N + HO{-}H$ (*vide supra*)
Ammonia + Water

Neurine † $\begin{array}{l} (O{-}H) < \\ \qquad | \\ Me_3 : N{-}(CH : CH_2) < \end{array}$ $Me_3N + HO{-}CH : CH_2$
Trimethyl-amine + Vinyl Alcohol

Choline $\begin{array}{l} (O{-}H) < \\ \qquad | \\ Me_3 : N{-}(CH_2{-}CH_2OH) < \end{array}$ $Me_3N{-} + HO{-}CH_2{-}CH_2OH$
Trimethyl-amine + Glycol

Muscarine $\begin{array}{l} (O{-}H) \\ \qquad | \\ Me_3 : N{-}(CH_2OH(OH)_2) \end{array}$ $Me_3N + HO{-}CH_2{-}CH(OH_2)$
Trimethyl-amine + Hydroxy acet-aldehydrol.

* Armstrong, *Journal of Chemical Industry*, July 30th, 1887.

† Me is the symbol for methyl, CH_3, and is used instead, so as to shorten and simplify the formula.

In these the trimethylamine takes the place of ammonia, and an alcohol takes the place of water.

Alcohols resemble water in their chemical structure, both containing hydroxyl (HO). In water this is combined with hydrogen and in alcohols with an alkyl, *e.g.*, ethyl, C_2H_5 or Et, thus :—

Water H—O—H

$$\begin{array}{l} \text{Ethylic} \\ \text{Alcohol} \end{array} \quad \text{H—O—Et} \quad \text{or} \quad \begin{array}{ccccccc} & & & \text{H} & & \text{H} & \\ & & & | & & | & \\ \text{H} & — & \text{O} & —\text{C}— & & \text{C} & —\text{H} \\ & & & | & & | & \\ & & & \text{H} & & \text{H} & \end{array}$$

Choline was first prepared from bile, and hence its name, but it may also be obtained easily from yolk of egg. In small doses it has no poisonous action. In large doses it has somewhat the same effect as neurine, but the lethal dose is ten times as great.

Comparison of Choline, Neurine, and Muscarine.

Choline, neurine, and muscarine resemble one another very much in action, though varying enormously in their toxic power, muscarine being much the most powerful. Possibly, also, though this point is not at all settled, choline and neurine have a certain tendency to paralyse the motor nerves and muscles in somewhat the same way as curare, although this power is not sufficient to interfere greatly with their other actions.*

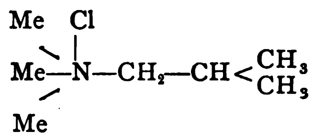
Relation between their Chemical Structure and Physiological Action.

From looking at the chemical structure of those alkaloids, one might imagine that they owed their poisonous activity to the hydroxyl group, but this is not the case, because two other substances, similar in structure, but without the hydroxyl, produce similar effects to muscarine, with the exception that they hardly contract the pupil at all.

* Neurine also produces fever in rabbits (Otto and Colmar, *Journ. of Phys.*, vol. viii., p. 218). I do not know whether the other substances do so or not, nor whether atropine prevents neurine from raising the temperature.

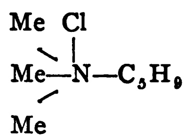
† Schmiedeberg and Harnack, *Arch. f. exp. Path. u. Pharm.*, Bd. vi., p. 112.

These are :



Isoamyltrimethyl ammonium chloride.

And :



Valeryltrimethyl ammonium chloride.

What is most peculiar, however, is that hexyltrimethyl ammonium chloride does not act like muscarine either on the heart or intestine.*

ACTION OF CHOLINE, NEURINE, AND MUSCARINE.

The effect produced by all three bodies may be shortly referred to one property, namely, their power of irritating the peripheral extremities of nerves going to secreting cells or to involuntary muscular fibres. By stimulation of the ends of the nerves going to glands they cause salivation, sweating, lachrymation, and increased secretion of the pancreas, liver, and mucous glands.

By irritation of the motor nerves going to involuntary muscular fibres they cause such muscles throughout the body to pass into a state of violent contraction, the pupil becomes contracted, and there is disturbance of vision, with spasm of accommodation; cramp-like spasms of the stomach and intestine occur, and cause vomiting and purging, and there is contraction of the bladder, spleen, and probably of the uterus. To this condition of increased contraction the heart forms a marked exception, because the cardiac branches of the vagus nerve contain in-

* Jordan (in Schmiedeberg's Laboratory), *Arch. f. exp. Path. u. Pharm.*, Bd. viii., pp. 16 and 30.

hibitory as well as accelerating fibres, and strong irritation of the vagus nerve produces slow action or complete stoppage of the heart. At first muscarine causes slight quickening of the pulse and flushing of the face, but this is soon followed by slowness, and in frogs the irritation of the vagus is so great that the heart will remain motionless in diastole for hours.

The respiration is embarrassed, and sometimes œdema of the lungs may ensue. This is ascribed by Von Basch to the disturbance of the cardiac action, but I am still inclined to think that contraction of the pulmonary vessels may be one factor in the respiratory embarrassment.

Antagonism of Atropine to these Poisons.

All the symptoms, whether produced by choline, neurine, or muscarine, can be rapidly and completely removed by atropine, which paralyses the identical nervous structures which are irritated by muscarine.

Structure of Atropine—Alkamines or Alkins—Tropine.

Choline and muscarine are built, as we have seen, on the ammonium type, in which pentad nitrogen is connected with an oxyalkyl and with alkyl groups; but another important class of bodies is built on the ammonia type, in which triad nitrogen is combined with an oxyalkyl and alkyl groups.

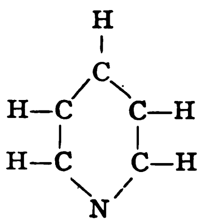
$\left.\begin{array}{l}H\\H\\H\end{array}\right\rangle N$	$\left.\begin{array}{l}CH_3.CH_2\\CH_3.CH_2\\CH_3.CH_2\end{array}\right\rangle N$	$\left.\begin{array}{r}CH_3.CH_2\\CH_3.CH_2\\HO.CH_2.CH_2\end{array}\right\rangle N$
Ammonia.	Triethylamine.	Triethyl Alkamine.

Alkamines are tertiary amines in which no H remains directly connected to N, for though they may be formed from secondary amines by union with oxyalkyl bodies, yet by the process the H is displaced and they become tertiary. Some of the most important of the alkins contain radicals belonging to the aromatic series. I have already mentioned that pyridine may be regarded as a tertiary amine, and one of the most important of the alkins, viz., tropine, may be regarded as derived from pyridine. Tropine

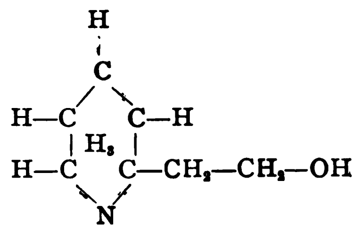
is the basis of atropine and of several allied bodies. It may be regarded as an oxyethyl-methyl-tetrahydropyridine,

$$C_5H_7(C_2H_4.OH)N.CH_3.$$

Its chemical structure has been represented thus :—



Pyridine.



Tropine.

Atropine—Tropeïnes—Homatropine.

Atropine is a compound of tropine with an acid—tropic acid—and is therefore tropate of tropine. By boiling with dilute hydrochloric acid it takes up water, and splits into tropine and tropic acid, and by uniting these bodies atropine is again formed. By combining tropine with other organic acids instead of tropic acid, a series of bodies has been formed, to which their discoverer, Ladenburg, has given the name of tropeïnes. One of the most important, in which oxytoluylic acid is combined with tropine, has received the name of homatropine. Tropine is the basis of both atropine and homatropine, but the acid is different, atropine being a tropate, while homatropine is an oxytoluylate of tropine.

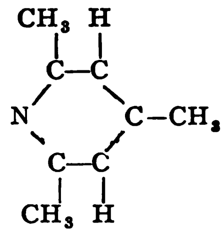
Relation of Ammonia to the Liver.

It is interesting to note that the ptomaines I have already mentioned are substituted ammonias, because, as we shall afterwards see, ammonia and some of its compounds have a very remarkable action upon the liver.

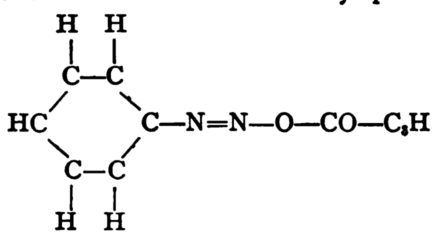
AROMATIC PTOMAINES.

You will have noticed that none of the ptomaines I have just mentioned contain any radicals of the aromatic group, although atropine

does. But other ptomaines do; indeed, the one which was first isolated by Nencki was collidine, which, like the others, contains three atoms of methyl, but associated with an aromatic nucleus.

Collidine— 

Another most important ptomaine appears also to belong to the aromatic series, for Vaughan thinks that the poisonous alkaloid of milk and cheese, which he discovered and named tyrotoxicon, is really butyrate of di-azo-benzene. The symptoms produced



Di-azo-benzene butyrate

by this alkaloid, which sometimes forms in milk during hot weather, are nausea, vomiting, headache, quick pulse, laboured breathing, constipation, and great prostration, with stupor. The pupils may be somewhat dilated, though not so much as in poisoning by atropine, and there may be also a scarlatina-like rash on the skin.

Practical Bearings of our Knowledge of Ptomaines.

High Game.

The practical outcome of the facts I have just brought before you is that there may be very great danger indeed of poisoning by alkaloidal substances formed in meat by its decomposition. Yet we know that while tainted beef is strongly objected to, high venison is looked upon as a delicacy, and the experiments of Bocklisch (p. 45) indicate that very probably the presence of two kinds of bacteria may be the cause of poisons being formed.

Tainted Meat.

Tracing the question a step farther, we ask : How are the two kinds of microbes likely to be present? And the simplest explanation is that the dangerous meat may have been got from a diseased animal, and the microbes present in its tissues may, by combining their action with that of ordinary putrefactive bacilli, have caused the formation of the deadly poisons. If this should be found to be the fact, it will clearly explain the necessity of avoiding as unfit for use the flesh of animals suffering even from the very earliest stage of acute disease. In high game, on the contrary, the tissues of the animal before death were healthy and free from bacilli, and the "highness" is only due to a single bacillus acting on the meat after death, and not producing any dangerous poison.

Atropine as a Possible Antidote.

The fact that choline, neurine, and muscarine are amongst the commonest products of putrefaction indicates the advisability of employing atropine as a remedy in these cases of poisoning, where the symptoms resemble those produced by these three bodies, and we may hope that ere long the risk of poisoning by milk or cheese may be lessened by an antidote to the tyrotoxicon being found, for a knowledge of its chemical nature indicates to us the direction in which an antidote is to be sought.

ACTION OF MICROBES IN THE INTESTINE.

Having considered the relation between disease and microbes living outside the body, we now come to discuss their action when they are taken into the intestinal canal, or applied to some absorbing surface, such as that of a wound.

Microbes in the Intestine.

Bacteria abound in the intestine even in health, and some have thought that they might even aid the digestive juices in breaking up the food. It is quite likely that they aid in breaking up the food, but whether they do so with any advantage to the organism may be somewhat questionable. They tend to split up the products of pancreatic digestion farther than the pancreatic ferment

would, and one of the substances to which they give rise is indol. This body has an antiseptic action, and belongs to the aromatic series, members of which, as I shall afterwards have to show, have a very marked action upon the liver. In the intestine it becomes converted into indican, which is absorbed and excreted in the urine.

Indican in the Urine.

When the quantity excreted is excessive it indicates that albuminous matters are undergoing rapid decomposition. Unless there is some other locality where such a process is going on, as in an abscess, it usually indicates that bacteria are active in the small intestine and, rightly or wrongly, I am accustomed to look upon much indican in the urine as an indication for a mercurial purgative, mercury being one of the most powerful antiseptics we possess.

Poisons formed during Digestion.

The presence of bacteria is not necessary for the production of poisonous alkaloids in the intestine, for fibrin digested with pepsin yields a substance to which its discoverer, Brieger, has given the name of pepto-toxine. This substance belongs to the aromatic series, and I shall have again to refer to it when speaking of the action of drugs upon the liver. It causes drowsiness and feebleness, and may possibly be the cause of the symptoms in some cases of indigestion, but it causes no diarrhœa.

Diarrhœa is, however, one of the most prominent symptoms produced by neurine, choline, and muscarine. Two other alkaloids—mydaleine, and another not yet named—which Brieger isolated from putrefying livers and spleens, have a still more powerful purgative action, producing almost continuous and fatal diarrhœa.

In all probability much of the diarrhœa which occurs, especially in children, after the use of milk, is due to the formation of tyrotoxicon, or other more or less poisonous products, by decomposition of the milk in the intestine itself. One of the most fruitful sources of diarrhœa in children is certainly the use of feeding-bottles with long tubes, which are generally imperfectly cleaned,

so that even when the milk is put quite fresh into the bottle it becomes inoculated with bacteria before it reaches the child's stomach, where the temperature is just right for their rapid multiplication and the decomposition of the milk. The difference between the chances of a child fed at the breast and in this way is enormous, for in the former case the milk flows free from germs directly into the child's mouth, and the risk of bacterial inoculation is greatly diminished.

Indeed, Andeer finds that in cows there is an antiseptic substance, resorcin, present in the udder, as if for the purpose of rendering the milk not only aseptic but antiseptic.

The possibility of contamination in the child's mouth itself suggests the advisability for careful supervision in regard to the cleanliness of things put into it, even though it only be the mother's fingers or a teething-ring.

There can be, I think, little doubt that choleraic diarrhœa, Asiatic cholera, and typhoid fever are all due to microbes, although bacteriologists may not have definitely settled the nature of the microbe in each case. In choleraic diarrhœa and cholera it is probable that the microbe acts to a great extent indirectly upon the organism by simply producing poisons in the intestine.

Cholera.

As I pointed out, in 1873, the symptoms of cholera are exactly those of muscarine poisoning, and most of the recent researches on the subject have tended to show that these symptoms are due to the action of a chemical poison which may act independently of the microbes which produce it. Lewis and Cunningham showed in 1874 that boiled cholera dejecta would still cause diarrhœa, although any microbe present in them must have been destroyed in boiling.* Cantani and Klebs have also obtained symptoms of poisoning from sterilised cultivations of the cholera bacillus. Pouchet obtained an oily base belonging to the pyridine

* "A Report of Microscopical and Physiological Researches into the Nature of the Agent or Agents producing Cholera." By T. R. Lewis M.B., and D. D. Cunningham, M.D., Calcutta, 1874, p. 56.

series from cholera stools, and Brieger got from pure cultivations of the comma bacillus in beef broth, in addition to the common ptomaines of putrefaction, two poisons which he regarded as specific products of the comma bacillus. But none of the poisons which have been isolated produce exactly the symptoms of cholera. In Cantani's experiments, tremor, prostration, spasms, and repeated vomiting were observed, while Klebs noticed muscular contractions and alterations of the kidney. The poison obtained by Pouchet irritated the stomach and slowed the heart, while one of Brieger's produced muscular tremor and cramps; the other lethargy, and feebleness of the circulation, with occasional bloody diarrhœa. These facts render it probable that the symptoms of cholera are not caused by a poison formed by the action of the comma bacillus alone, and it is evident that much more extended investigation is required before the pathology of cholera is accurately understood.

In all such investigations, too, one must bear in mind the possibility of the poison being formed not in the intestines merely, but in the blood or tissues.

Typhoid Fever.

In typhoid fever the symptoms do not point so much to the formation of a poison affecting the body generally, as to the local action of the microbes upon the intestine, although in some epidemics of typhoid the intestinal symptoms are but slightly marked, while bronchial irritation is very prominent. Whether this bronchial irritation is due to the action on the bronchial mucous membrane of a microbe or of a ptomaine produced by it, I cannot say.

TREATMENT OF DISEASES DEPENDING ON MICROBES IN THE INTESTINE.

Coming now to the treatment of diseases depending upon microbes in the intestine, it is evident that the indications are:—

Firstly, to remove both the microbes and the poisons they have formed as much as possible (*Eliminative Treatment*).

Secondly, to prevent or lessen the growth of any microbes which may still remain in the intestine, and prevent their forming any more poisons (*Disinfectant or Germicidal Treatment*).

Thirdly, to neutralise the injurious effects of any poisons already absorbed into the blood (*Antidotal Treatment*).

Eliminative Treatment.

It is curious to watch the changes in medical theory and medical practice, and I remember, when a student, being told that the prompt administration of an emetic would sometimes cause an attack of infective disease to abort. This method of elimination has now fallen into disuse, but the present state of our knowledge seems to show that it may not have been without its uses, and it may again be revived. The treatment of diarrhœa by purgatives is still largely followed, and with great advantage. In many cases, if we try to lessen the diarrhœa at once by the administration of chalk or opium, we only make matters worse, whereas a dose of castor-oil with a few drops of laudanum in it, just sufficient to lessen the irritation and not to interfere with the purgative action of the oil, will often put an end to the attack.

It is interesting to notice here, also, how modern researches appear to explain the empirical use of cinnamon water in the chalk mixture with which the dose of castor-oil is so frequently followed up. Cinnamon water no doubt contains a small quantity of tannin, which may have a somewhat astringent action; but the essential oil is probably its most important ingredient. This belongs to the aromatic series, and is probably a good antiseptic; while the oil of cloves, which along with cinnamon, is an important ingredient of aromatic chalk powder, is an antiseptic of considerable power. Oil from one species of cinnamon (*Cinnamomum Culilowan*) is regarded in the Molucca Islands as a powerful astringent in cholera.* Another common treatment of diarrhœa is the administration of camphor, which is a powerful antiseptic.

* Husemann, *Arzneimittellehre*, 2te Aufl., p. 570.

Modifications in Treatment necessitated by the Action of Antiseptics on the Organism.

It is evident that, while we can employ antiseptics outside the body without regard to anything but their power to destroy microbes, yet when we use them for intestinal disinfection, we are obliged to consider the effect that they may produce upon the organism.

When the contents of the stomach are undergoing decomposition, either from yeast, sarcinæ, or bacteria, we may get good results by the use of creasote or carbolic acid, because these substances come directly into contact with the microbes in the stomach, and a quantity of them which is too small to be injurious to the patient will be sufficient to act as a disinfectant. If the intestine is to be disinfected, these drugs will not produce this effect so readily, because they will be partly absorbed in the stomach, and one has to look either for some remedy which on account of its sparing solubility will pass through the stomach into the intestine without being absorbed, or else one which will not have much poisonous action.

Intestinal Disinfectants.

Several remedies have lately been proposed as intestinal disinfectants. Naphthaline, which has been recommended by Rossbach,* is very sparingly soluble, so much so that it passes to a great extent unchanged through the whole of the intestinal canal. It certainly destroys the disagreeable odour of the motions in infantile diarrhœa, but it does not appear satisfactorily to check the disease. Salol is the phenyl ether of salicylic acid or salicylate of phenyl. It passes through the stomach unchanged, but in the duodenum it is split up by the pancreatic juice into salicylic and carbolic acids. Although the carbolic acid is set free at the point where its action is wished, yet there is still the disadvantage of its being poisonous, and so betol or salicylate of β napthol has been recommended. The constitution of this substance is similar to that of salol, but it splits up into salicylic acid and beta-naphthol, which is much more sparingly

* Rossbach, *Berl. klin. Woch.*, 1889, No. 42.

soluble, and which is less poisonous than carbolic acid, while it is much more powerfully antiseptic. Resorcin, thymol, and benzoate of soda are among the antiseptic remedies which sometimes are useful, but these are either weak or subject to the same objections as carbolic acid.

Direction in which to look for Intestinal Disinfectants.

When we consider the enormous number of aromatic compounds which have an antiseptic action, we may expect almost with certainty that amongst them most useful remedies are to be found for diarrhœa, and Pellicani has found that substances containing a *diphenyl** nucleus are less poisonous, and at the same time more powerfully antiseptic, than those containing a single phenyl nucleus.† This class of bodies is evidently one in which we ought to search for intestinal antiseptics. But it is quite possible that some of these bodies, otherwise well suited to our purpose, may, like phenol, have an injurious action upon the organism, and the question arises whether this could not be obviated. Phenol and a very large number of the bodies allied to it are excreted in the urine as sulphates, or, to speak more correctly, as ethers of sulphuric acid, that is, as sulphuric acid in which one atom of the hydrogen has been replaced by the aromatic radical. Such a combination with sulphuric acid seems to destroy to a great extent the poisonous action of these phenyl compounds upon higher organisms, and by the administration of sulphates the poisonous effect of carbolic acid can be to a great extent neutralised.

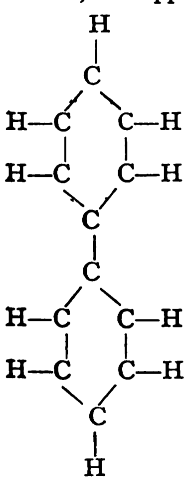
Phenyl-sulphuric acid, or sulpho-carbolic acid, forms salts with bases, and these salts, though somewhat less powerful disinfectants than carbolic acid, are not nearly so poisonous. They were introduced into medicine in 1869 by Dr. Sansom, and have proved of considerable value as intestinal disinfectants.

As I mentioned before, the diphenyl compounds seem to have less toxic action than those containing a single phenyl group, and possibly the best direction to look for new intestinal disinfectants would be amongst the sulpho-compounds of the diphenyl group.

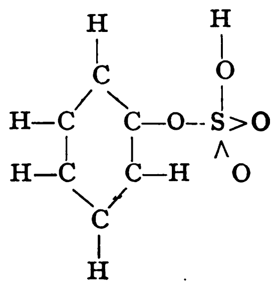
* *Vide* pp. 33 and 68. † Pellicani, *Arch. per le Scien. Med*, vol. vi., p. 113.

Sulphonic Compounds: Aseptol.

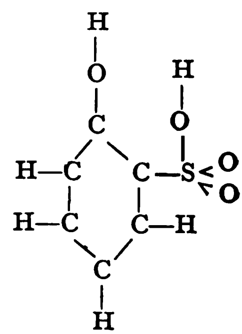
But there is another class of sulpho-compounds, the sulphonic compounds, in which the atom of sulphur, instead of being united by means of oxygen to the aromatic nucleus, is attached directly to one of the carbon atoms in that nucleus. One such compound, ortho-phenol-sulphonic acid, sozolic acid, or aseptol, as it has been christened, has been introduced both as a local antiseptic and as an intestinal disinfectant. The commercial aseptol is a solution containing one part in three, and it is administered internally, in the same dose as salicylic acid, in cases both of gastric and intestinal catarrh, and apparently with good results.



Diphenyl.



Phenyl-Sulphuric Acid.



Aseptol.

STARVING OUT BACTERIA.

Another indication for treatment, besides removing the microbes or destroying their activity, is to starve them out. Although microbes may be able to digest both albuminous and starchy matters—and they may adapt themselves to a certain extent to altered nutrient media, so that when accustomed to grow upon albuminous matters they may learn to grow on starch and *vice versa*—yet their action upon the new foods is not so great as that upon those to which they are accustomed.

Escherig has shown that the bacteria usually present in the intestines and stools of young children fed upon milk completely disappear when milk is stopped and a meat diet is substituted. This explains why the use of pounded raw meat or its juice is occasionally so useful in infantile diarrhœa. It is evident that if the bacteria should begin to thrive in the intestine on a nitrogenous diet like this, it must be changed, and the bacteria starved out by substituting rice water or some such farinaceous food.

In Infantile Diarrhœa.

For this reason Vaughan recommends that in infantile diarrhœa the administration of milk should be entirely stopped, as it simply affords nutriment to the bacteria, and is decomposed by them with formation of poisonous substances. In place of it, beef-tea, rice-water, or pure water should be given, and this should be kept up for some days until the milk bacteria have probably died out. Thus we find that the most recent researches bring us back to the practice of Sydenham.

In Typhoid Fever.

The same question comes into consideration in regard to typhoid fever. In the treatment of cases of this disease some years ago, I occasionally allowed farinaceous food rather early, say at the end of the second week, because I thought that if properly softened it could not produce any mechanical irritation upon the intestine, however much ulcerated it might be. But several times the temperature seemed to rise so distinctly after the farinaceous food that I began to be very chary of allowing it, and the only explanation that I could think of was that, somehow or another, it might afford a more favourable nutrient medium to the bacilli.

MICROBES IN SEROUS CAVITIES AND IN WOUNDS.

Other cavities of the body, such as the bladder, uterus, pleura, and peritoneum, may serve, like the intestinal canal, as a place where microbes may grow and form poisons. The same rules as to absorption apply to them as to the intestinal canal, and dis-

infectants must either be sparingly soluble or not powerfully toxic. This is also the case with wounded surfaces, at least, if the disinfectant is to be kept in constant contact with them, for they absorb rapidly, and, moreover, the antiseptic must have little or no local irritant action. Carbolic acid has the twofold advantage of having a slight local anæsthetic action and being at the same time a powerful antiseptic, but a number of instances of poisoning by its absorption either from wounds or closed cavities into which it has been injected having occurred, surgeons have been for some years looking out for another antiseptic which would possess all its advantages without any of its disadvantages. In this search they have for a time forsaken carbon compounds, and have resorted to the use of mercurial salts, to some extent at least; but yet, at the same time, a number of new organic substances have been under trial, and have been more or less successful.

Halogen Compounds as Antiseptics.

Chloroform—Iodoform.

Chlorine, bromine, and iodine in their free condition are amongst the most powerful antiseptics we possess, and it seemed likely that the organic compounds containing them in large quantity would have an antiseptic action. Accordingly, iodoform (CHI_3), which corresponds in its chemical structure to chloroform ($CHCl_3$) (itself an antiseptic), but which contains iodine in place of chlorine, was tried, and for a while was much praised. But further trials have shown that it is by no means as powerful an antiseptic as carbolic acid, and is perhaps even more dangerous than it. Its special advantages were supposed to be that the iodine which it contained was only set free by living protoplasm, and thus it might act as an antiseptic and kill microbes, just like sulphur. Though sulphur itself is an inert powder, it destroys the fungus of the vines on which it is sprinkled, because from it the protoplasm of the fungus forms sulphurous acid or sulphuretted hydrogen, by which it is itself destroyed. When sprinkled on a wound iodoform prevents the

movements of leucocytes, renders the surface dry, prevents suppuration, and encourages granulation, while at the same time its local anæsthetic action lessens pain. It seems to have a special destructive action on the tubercle bacillus, and is therefore employed with advantage as a local application for tubercular disease of the larynx and tubercular abscesses. One great convenience of iodoform consists in the fact that it can be applied as a powder over any surface, and will there exercise its antiseptic action for a long time without the necessity of any dressing being applied over it, but as I have said, it is not without its dangers, and although sparingly soluble, it may yet be absorbed from wounds or cavities to such an extent as to produce poisoning. The symptoms of poisoning are particularly interesting, as they consist of a peculiar combination of the action of iodine itself with that of an alkyl. Like an iodide, it may produce unpleasant taste and smell, running at the nose, and gastric disturbance, but it behaves also like a member of the alcoholic series in causing special symptoms of poisoning which are connected with the nervous system, and consist of loss of memory, variable temper, headache, sleeplessness, and especially mental disturbances, sometimes amounting to furious mania, alternating with coma. Fatty degeneration of the heart and other organs is usually found after death.

Iodol.

On account of this poisonous action of iodoform, another organic compound of iodine has been introduced. In this the proportion of iodine is somewhat smaller, and the carbon compound with which it is combined, instead of belonging to the alcoholic or open-chain series, belongs to the class intermediate between it and the aromatic series. In it four carbon atoms along with one of nitrogen form a closed ring, and to this four atoms of iodine are attached. This body, iodol, is a yellowish powder, which can be used exactly like iodoform. It has over iodoform the advantage of being free from any disagreeable odour, and of being less poisonous. In animals, however, it produces in large doses symp-

toms similar to those of iodoform, and it has the disadvantage of being somewhat more irritant locally.

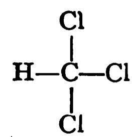
Sozoiodol.

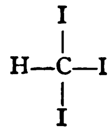
As the antiseptics I have already mentioned, although useful, are not without their disadvantages, one would naturally look for something else which might be free from them, and one of the first ideas which would occur to a chemist would be to combine the iodine with some compound of the aromatic series instead of one of the fatty series, as in iodoform, or of the intermediate series, as in iodol. This has been done, and a large number of preparations have been introduced under the name of sozoiodol. This is a compound of iodine with paraphenol-sulphonic acid, which only differs from sozolic acid, or orthophenol sulphonic acid, which I have already mentioned, in the position of the hydroxyl and sulphonic groups. Sozoiodol forms salts like phenol, the hydrogen in the sulphonic group being replaced by a base. The salts chiefly used have been those of sodium and potassium, and they have been employed either in watery solutions, or mixed with talc or sugar of milk as powders in place of iodoform, or in the form of ointments. Like iodol, they have the advantage over iodoform of being without smell, and, so far as experience has yet gone, they produce no poisonous effect.

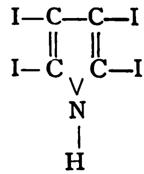
Chlorine Compounds.

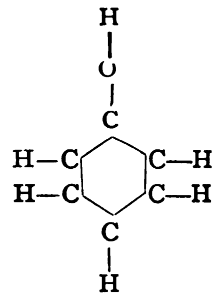
Another natural idea is to combine chlorine instead of iodine with phenol, and this has been tried. Trichlorphenol contains three atoms of chlorine in place of three of hydrogen. It has a somewhat disagreeable odour, it is almost insoluble in water, but forms salts, and those of calcium and magnesium have been found to be not only powerful disinfectants, but to have no irritating action on the tissues.

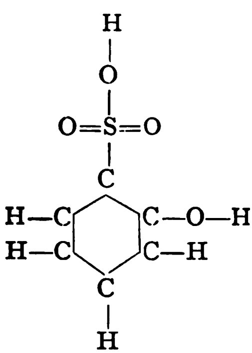
The relation of these antiseptics will be evident from a comparison of their graphic formulæ.

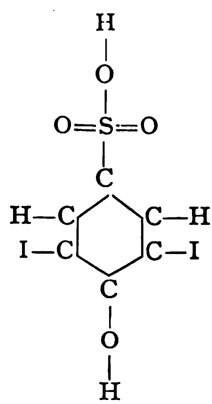

Chloroform.

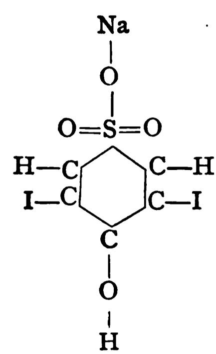

Iodoform.

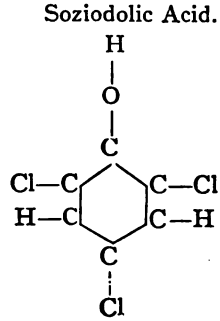

Iodol.


Phenol.


Sozolic Acid
(Aseptol).


Soziodolic Acid.


Soziodolate
of Sodium.


Trichlorphenol.

ANTISEPTICS IN LOCAL DISEASES.

The application of germicides is not only useful in cases where the microbes form poisons, which by their absorption may cause general poisoning, but is also of service where the microbes pro-

duce only local mischief. Thus, resorcin and iodoform have been of great service in the treatment of skin diseases, such as lupus, where the disease appears to depend upon, or at least to be constantly associated with, the presence of a bacillus. In such diseases it is easy to remove such parts of the tissue as have been completely infiltrated with the microbes, and also at the same time to apply the remedy freely to the part affected. Even malignant disease has been said to yield to the influence of local antiseptic treatment, and a spindle-celled sarcoma of the tonsil is said to have disappeared under the action of iodoform, although confirmation of such a result is desirable.

Treatment of Consumption.

The most important result which could be obtained by the local use of antiseptics would certainly be the cure of consumption, and numerous have been the attempts to destroy the tubercle bacillus in the lung by means of antiseptic remedies, either inhaled or conveyed to the lung through the blood. Carbolic acid, salicylic acid, aromatic oils of various sorts, and especially eucalyptus oil, have been employed as sprays or inhalations, and iodoform has both been inhaled and applied by insufflation, especially in cases where the tubercle has affected the larynx. In laryngeal phthisis these insufflations are certainly of use, and even where the disease affects the lung a certain amount of amelioration of the symptoms has followed the use of antiseptic measures. It has not been shown that any real cure has been effected by them, and this is not at all wonderful when we consider the difficulty of applying them locally in such a way as to destroy the bacillus without affecting the delicate structures of the lung itself. But the idea seemed feasible that one might be able to introduce into the blood some substance which, during its excretion by the lung, would have an antiseptic action and destroy the microbes without damaging the pulmonary tissues.

Enemata of Sulphuretted Hydrogen.

Accordingly, the treatment of phthisis by enemata, containing sulphuretted hydrogen diluted with carbonic acid, was suggested

and largely employed for a short time. It was stated by Claude Bernard that sulphuretted hydrogen is very rapidly eliminated by the lungs; so rapidly, indeed, that hardly any passes into the left side of the heart and the arterial system. Therefore the risk of poisoning by enemata of the gas ought to be very small; yet Orfila had shown, many years before, that enemata of sulphuretted hydrogen might cause poisoning very rapidly. A case of poisoning by the formation of this gas in the intestines has been recorded by Senator, and experiments by Cash and myself on the absorption of gas from the intestines confirmed Orfila's results.* The practice, therefore, seemed not to be without risk, and the occurrence of a fatal case, as well as the smallness of the beneficial results which have been obtained from it, have caused the practice to fall into disuse.

Non-gaseous Antiseptics.

The principle, however, appears to be rather a good one, and the direction in which one would now look is for some substance which would undergo slow decomposition in the intestine or in the body generally, and give rise to volatile antiseptic products which would be slowly but constantly eliminated by the lungs, so that during the whole twenty-four hours the tubercle bacilli would be exposed to its action. Though a volatile substance which would be excreted by the lungs is most likely to be beneficial, yet perhaps it is not absolutely necessary that it should be volatile. A soluble substance circulating in the blood might be efficacious if it possessed a specific power to destroy the tubercle bacillus without injuring the tissues of the lung or acting as a poison to other organs of the body.

Camphors—Helenine—Alantic Acid.

Such properties are said to be possessed by helenine, which M. Korab found to destroy tubercle bacilli when kept in contact with them. This is a form of camphor which occurs along with alantic oil and alantic acid in the root of elecampane (*Inula helenium*).

Like other forms of camphor, these are all antiseptics, arresting putrefaction, but having in addition a special power to destroy

* Lauder Brunton and Cash, St. Bartholomew's Hosp. Reports, 1886, p. 302.

tubercle. The experiments of Marpmann appear to show that the latter two substances may possibly be useful, as animals to which they were administered did not die when inoculated with tubercle, while others, similarly inoculated, and which did not receive the medicine, died. They have no injurious action upon man, and after their prolonged administration to phthisical patients the tubercle bacilli disappeared from the sputum. In cases of phthisis where I have prescribed helenine the patients appeared to improve, the dose employed being three grains or more in the form of pill.

Phenyl-acetic and Phenyl-propionic Acids.

In a most suggestive paper by Dr. Burdon Sanderson he mentioned the destructive effect which phenyl-acetic and phenyl-propionic acids had been shown by Klein and Lingard to exert upon the bacillus tuberculosis. In consequence of this Dr. Theodore Williams tried these substances in cases of phthisis, and apparently with very good results. They may, however, sometimes cause sickness and discomfort in the patient, and are not quite so well borne as helenine. Further trials are required in order to establish the utility of any of these substances, and to ascertain whether other remedies, having a similar character, may not be discovered and found to be more efficacious.

ACTION OF MICROBES IN THE BLOOD AND TISSUES.

We may now turn from the consideration of microbes and their action when in contact with mucous membranes or raw surfaces to their effect after they have gained an entrance into the circulation. The bacilli of anthrax and of septicæmia in mice probably produce their effect chiefly in the blood, while other poisons, such as those of measles, rötheln, scarlet fever, small-pox, acute rheumatism, and tetanus, probably act more upon the tissues. Various theories have been proposed as to the mode in which the anthrax bacillus causes death. One idea is that the bacilli, by aggregating together, block the capillaries and cause embolism; a second is that they produce a ferment which decomposes the tissues; a third is that they give rise to one or more definite poisons. It is quite possible that all these theories may be to a certain extent correct, and that each of

them may represent one factor in the production of the symptoms. The third of them is probably the most important, however, and the symptoms probably depend chiefly upon the formation of a poison. Indeed, Hoffa has obtained from pure cultures of the bacillus anthracis a ptomaine which produces the symptoms of anthrax, and death when subcutaneously injected; but it is not unlikely that the presence of a ferment may aid the anthrax bacillus in the production of a poison. Wooldridge claims that he has transmitted the toxic power of anthrax to vegetable albumen, organisms being absent. Pasteur showed that the anthrax bacilli did not produce a ferment which was capable of causing the disease when injected, for by filtering the blood of animals suffering from anthrax through porous cylinders, and thus keeping back the bacilli, he obtained a filtrate which was inactive. In all probability, any ferment which the bacilli had formed would have passed through in the filtrate, and would have produced the ordinary symptoms after injection; but Nencki proved this in a way still more free from objection, for he inoculated gelatine jelly with anthrax bacilli. These liquefied the gelatine, and fell to the bottom, and the clear liquid which remained above produced no effect on animals.

These experiments appear to prove that if the anthrax bacilli produce a ferment at all, it is incapable of producing the disease. At the same time one must remember that after the injection either of the vegetable ferment, papain, or of sterilised septic blood into animals, Rossbach and Rosenberger found their blood swarming with bacilli. This observation seems to show that the ferment had rendered the blood more suitable for the rapid growth and multiplication of the bacilli.

Puerperal Fever.

In puerperal fever it is probable that the production of ptomaines in the tissues plays an important part, for Bourget isolated several toxic bases from the viscera of a woman who had died of this disease. This would not by itself prove that these poisons had been formed during life and were not simply the products of putrefaction, but he also obtained from the urine of

patients similar bases which were highly toxic, and killed frogs and guinea-pigs when administered by injection. The amount of poison in the urine was greatest when the symptoms were most severe, and diminished when the patients recovered. This fact appears to indicate a connection not only between the poison and the disease, but between the gravity of the disease and the amount of poison.

Tetanus.

The pathology of tetanus was for a long time doubtful, and it was frequently ascribed to reflex excitability of the nerve centres due to the irritation of the cicatrix. It is now shown to be in all probability dependent on a bacillus present in earth or other matter contaminating a wound. The difficulty of thoroughly cleansing the infective matter from slight punctures, and the risk of wounds about the hand becoming afterwards infected even when thoroughly cleansed at first, explains why tetanus should so frequently follow very trivial injuries.

When animals are inoculated with matter taken from suppurating points, or with the medulla of animals which have died of tetanus, the disease is reproduced, and on microscopic examination a bacillus has been found to be present. From pure cultivations of this bacillus Brieger obtained four poisons. The first, tetanine, produces tetanus in mice when injected in minute quantity. Another, which he has not named, also causes tetanus, along with a free flow of saliva and tears. Another, tetanotoxine, first produces tremor, then paralysis, and lastly violent convulsions. A fourth, spasmotoxine, causes severe convulsions both clonic and tonic. This discovery of Brieger's renders it probable that the convulsions in tetanus are due to the action of a poison, but we cannot at once assume that this poison necessarily circulates in quantity with the blood, especially as the flesh of animals which have died of the disease may be eaten with impunity.* It is quite possible that it may be formed either entirely or chiefly in the nerve centres, and that only very small quantities of it pass into the general circulation.

* Sormani, *Rendiconti del Reale Instituto Lombardo*, March 28th, 1889, quoted in *Nature*, May 2nd, 1889, p. 21.

Hydrophobia.

In hydrophobia this is very probably the case, and Anrep says that he has isolated a ptomaine from the brain and medulla oblongata of rabbits suffering from a severe form of rabies. This ptomaine is very poisonous, and minute doses cause the earlier symptoms of rabies, while large doses cause the phenomena usually observed in the latter period of the disease. A gradual habituation of the animal to small doses of the ptomaine produced a certain degree of immunity.*

Diphtheria.

From cultivations of diphtheria Roux and Yersin have obtained a soluble poison which may cause the symptoms of diphtheria in various degrees of intensity according to the dose. A large dose may cause rapid death, a smaller one may produce paralysis, ending fatally, while a still smaller one may cause only temporary paralysis.†

This poison, however, is not a ptomaine, that is, it is not of an alkaloidal nature. It appears to be rather allied to enzymes or to albumoses, and is destroyed by boiling for ten minutes. The results of experiments already made render it hopeful that it may be possible by its means to confer immunity from the disease, but this is not yet certain.

TREATMENT OF DISEASES DEPENDING UPON INFECTION OF THE BLOOD OR TISSUES BY MICROBES.

There are two lines of treatment which one would naturally pursue. The first is to destroy the *microbes*, or weaken them so that the leucocytes of the blood or the cells of the tissues may be able to complete their destruction.

The second is either to eliminate the *poisons* they have formed or to use some remedy which will antagonise their action.

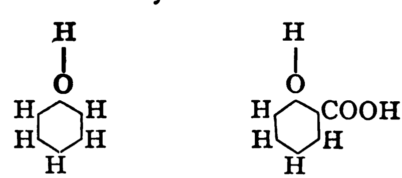
The difficulty of destroying microbes by drugs is still greater in the circulation and tissues than it is in the intestinal canal or in

* Anrep, *Vratch*, No. 2, 1889, p. 52, abstracted in the *Brit. Med. Journal*, Feb. 9th, 1889, p. 319.

† Roux and Yersin, *Annales de l'Institut Pasteur*, 1888, Nos. 11 and 12.

any of the body cavities; for here the comparative solubility of a remedy will not help us. We require one which will destroy the microbes without injuring, or at any rate without injuring to any great extent, the cells of any of the tissues, for it will be carried to them all by the blood. It is quite clear that if the microbes are few in number, so that the fight between them and the leucocytes or tissue cells is a fairly even one, the balance may be turned by the use of a drug which will hurt the microbes more than the organism. Even if it should be somewhat injurious to both, the quantity required to kill the microbes will do the organism no great harm, and the total result will be a cure; but if the microbes are very abundant the antiseptic dose required to destroy them may be so great that it would of itself be poisonous to the diseased animal. We can thus see that experiments with the same remedy may yield very different results in the hands of different observers, and that while some might laud it as a certain cure, others might regard it as of no use whatever. From its general antiseptic power carbolic acid was likely to be the remedy first tried, and Bouley, Davaine, and others employed it in cases of anthrax with a certain amount of success.

Salicylic acid, which is closely connected with carbolic acid in its



Phenol or Carbolic Acid. Salicylic Acid.

composition, differing from it by the introduction of the carboxyl group (COOH), has also been tried in a great number of infective diseases. In most of them it has been of little use, but in acute rheumatism it certainly lessens the pain and reduces the temperature, giving the patient great relief. Whether it cuts short the disease, however, is a question which is not yet finally settled, although possibly the difference in opinion on this subject may be partly due to the different modes in which it is administered. It is evident, however, that amongst the enormous numbers of anti-

septic compounds we may yet expect to find many drugs which may be useful as disinfectants in the blood and tissues.

Treatment by Elimination: Purgation: Diuresis.

Another method consists, as I have mentioned, in increased elimination. Free purgation was formerly resorted to, and apparently in many instances with good results, nor is this to be wondered at when we learn that fæces contain large quantities of ptomaines as well as of microbes.

But the most ready channel for the elimination of soluble poisons is the urine, and diuretics have long been used in the treatment of febrile diseases, and are still trusted as amongst the most efficient remedies. Acetate of ammonia and spirit of nitrous ether are still amongst the most favourite remedies as antipyretics.

Washing Poisons out of the System.

One of the best diuretics is a free supply of water, and Ringer pointed out the possibility of lessening the effect of poisons by washing them, as it were, rapidly out of the system.* This plan has recently been followed by Sanquirico † with very striking results. In his experiments he injected quantities of a weak saline solution directly into the veins, immediately after the poison had been administered, or just when the symptoms of poisoning began to appear. By treatment in this way he found that three times the ordinary lethal dose of strychnine had to be administered before death occurred. The poisonous action of chloral, alcohol, urethane, paraldehyde, caffeine, and aconitine was also diminished, but not very much, while that of morphine and nicotine was unaffected. In all cases the beneficial effect of the treatment was most marked when the diuresis was greatest. No doubt the effect of fluids is likely to be greater when they are introduced directly into the veins than when they are introduced indirectly

* Ringer, *Lancet*, 1883, April 14th, p. 628; Murrell, *ibid.*, April 21st, p. 705.

† Sanquirico, *Centralbl. f. d. med. Wiss.*, 1886, p. 929; and *Arch. per le Scienze med.*, vol. xi., p. 275.

through the alimentary canal, but the effect in both cases will be the same in kind, though different in degree. I think we sometimes follow this plan unwittingly in febrile diseases by feeding the patient on milk, and more especially on milk diluted with soda and potash water. We thus administer a larger quantity of liquid than we should otherwise be likely to do, and the carbonic acid in the effervescing water tends both to aid absorption from the stomach and to stimulate excretion by the kidneys.

LEUCOMAINES.

With the exception of peptotoxine, which is formed by the action of pepsine, I have hitherto spoken of alkaloids which owe their formation to microbes, and which are called ptomaines. But the cells of living organisms also break down albuminous matter in the course of the functional activity, and alkaloids are formed in the healthy body, to which the name of leucomaines has been given. An interesting observation has been made by Bouchard, to the effect that the alkaloids formed during sleep have a stimulating action, so that when they accumulate to a certain extent they tend to excite the nervous system and make the person awake. Those, on the other hand, which are formed during the waking hours have a depressant action, and tend to bring about a condition of sleep. There is thus a sort of self-regulation in the processes of life, by which waking and sleeping are alternately ensured. To this point, however, I shall have to refer again in considering the action of soporifics.

Uræmia.

In health all the poisonous substances formed during tissue-change are excreted chiefly in the urine; but when the kidneys are diseased, or have been in any way rendered functionally inactive, these poisons may accumulate and give rise to those symptoms of poisoning which are usually known by the name of uræmia. In cases of disease of the kidney where such a condition has been threatening, an exclusively milk diet proves of the greatest service, and probably does so in a great measure by washing the poisons out in the way I have just mentioned, although it is also likely that such a diet tends to limit their production.

Bearing of Chemical Structure on the Treatment of Uræmia.

The objection may be raised that in a good deal of what I have just been saying there is no very obvious relation to chemical constitution. This is quite true, because, though Brieger has pointed out that most of the alkaloids that he has obtained are either amines or diamines, or else more complicated compounds of nitrogen and carbon allied to uric acid, yet the chemical structure of many of those formed in the body either in health or disease has yet to be discovered. When we know their chemical nature we may be able, in a case of uræmic poisoning, at once to administer an antagonistic remedy and save our patient, instead of standing, as at present, almost helplessly by. A knowledge of the relation of chemical structure to physiological action is likely to guide us also in our investigations regarding the nature of the poisons in uræmia. One set of poisons is probably allied to uric acid, and may include guanidine, methylguanidine, and other derivatives of urea.

Urea, Uric Acid, and Oxalic Acid as Waste Products.

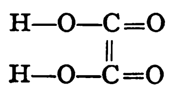
In health the greatest parts of the products of albuminous waste are excreted by man in the form of urea; uric acid occurs only to a small extent. But in various disturbances of nutrition we find that the quantity of uric acid is greatly increased, and that sometimes along with it oxalate of lime makes its appearance. We might, therefore, naturally look for compounds of oxalic acid as among the substances likely to give rise to symptoms of poisoning if retained in the body.

Symptoms of Uræmia.

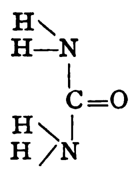
For my own part, I have sometimes been struck with the extremely rapid pulse in cases of uræmia, although there was no rise of temperature to account for it. This rapidity could hardly occur unless the vagus were either paralysed or inactive, and resembled so much the effect of atropine that I have been inclined sometimes to think that an atropine-like body was giving rise to the symptoms.

Hypothesis as to the Nature of the Poison in Uræmia.

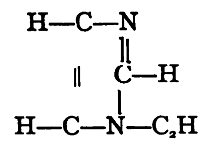
Now there is a substance allied in its chemical constitution to oxalic acid, namely, oxalethylene, which has the power of paralysing the vagus and producing great rapidity of the pulse, just like atropine, which it also resembles in its action upon the pupil and brain, dilating the pupil and exciting the brain.



Oxalic acid.



Urea.



Ethyl-glyoxal-ethyline or Oxalethylene.

When one atom of hydrogen in this body is replaced by chlorine so as to form chlor-oxal-ethyline, we obtain a body which no longer dilates the pupil and acts upon the brain like morphine, but still paralyses the vagus. We thus have a group of symptoms which closely correspond with those occurring in certain cases of uræmia. Should this substance, or any one nearly allied to it, be found to be present in cases of uræmia, experiments could readily be instituted with a view of finding antagonistic compounds, and the end we desire might be attained. In some cases of uræmia the injection of pilocarpine has arrested the convulsions, and it appears to me more likely to have produced these effects by antagonising a convulsing poison than simply by producing profuse sweating, although such an action might possibly tend to help elimination. This appears to be more likely from the observation of Sänger that pilocarpine is only of use before the occurrence of coma, for this symptom probably indicates either the presence of another alkaloid not antagonised by pilocarpine or an accumulation of poison to an extent which cannot be neutralised.

In Fraser's experiments on antagonism he showed that, while atropine and physostigmine counteracted each other up to a certain point, yet when the dose was too great the presence of both appeared to cause death more quickly even than either the one or the other alone.

PREVENTIVE TREATMENT OF INFECTIVE DISEASES.

In the early part of my lectures I mentioned that just as we can prevent the growth of a crop by destroying the seed or rendering the soil barren, so we may prevent the occurrence of infective diseases either by destroying the microbes which form the disease germs or by altering the soil, *i.e.*, the organism, in which they are to grow. We read in history of an ancient custom of rendering the soil of an enemy's city, which had been razed to the ground, barren and waste by sowing it with salt, and in our own day we see a similar plan made use of to prevent the growth of grass and weeds on gravel walks. The beneficial results of vaccination for small-pox has shown the possibility of sterilising the organism for particular microbes, so that they could no longer thrive in it; and Pasteur's treatment of anthrax with a weakened virus has induced men to ask the question, How is insusceptibility to disease induced? and to try whether it was possible to prevent disease by the administration of chemical substances instead of by inoculation with microbes. One of the most powerful of all disinfectants is corrosive sublimate, and it has the advantage of exerting its antiseptic powers in all kinds of liquids. Koch used it, but without success, as a cure for anthrax, administering it after the disease had already been established. Cash administered it to animals as a preventive, and found that those which had received it for some time before inoculation remained well, while those not so treated died after inoculation. The possibility of preventing infective disease by the administration of remedies was thus proved. Pasteur, with the prophetic insight of true genius, arrived at the conclusion that the active agent in preventing hydrophobia was a chemical substance formed by a microbe and not the microbe itself, and upon this idea his plan of preventing hydrophobia is based. Wooldridge found that when anthrax bacilli were cultivated in beef broth, and the bacilli themselves were removed by filtration, the filtrate containing, as it did, the products which they had formed during their growth rendered an animal into which it was injected proof against anthrax inocuated afterwards. Pasteur and Perdrix found that the blood of animals suffering from anthrax when sterilised and injected into

rabbits appeared to protect them against subsequent inoculation. Chantemesse and Vidal have found that the administration of sterilised cultures of the typhoid bacillus protects against subsequent inoculation with the germs, and similar results have been obtained by Roux and Chamberland in regard to septicæmia.

Salmon and Smith have found that a similar treatment with a sterilised culture of the hog bacillus will protect pigeons against inoculation of the said disease, but they have not yet succeeded in protecting pigs. Lately, also, Pasteur and his assistants have succeeded in cultivating the organism which gives rise to diphtheria. They find that the poison which it produces is most virulent, so that an exceedingly minute quantity of it will produce death. Like the disease itself, this poison will produce paralysis of motor nerves, and it seems probable that the symptoms of the disease are, to a great extent, due to the absorption of the poison from the surface of mucous membrane upon which it is formed. This poison appears not to be of an alkaloidal nature, but rather of an albuminous character, and it is allied to ferments by the fact that it is quickly destroyed by boiling. Inoculation with minute doses of the poison, gradually increased in quantity, will finally not only render an animal insusceptible to the large quantities of the poison, but protect it against diphtheria when the disease germs themselves are afterwards inoculated.

Mode of Action of Preventive Inoculation.

The tolerance of poison which has been established in the case of diphtheria is probably similar in its character to what occurs during the habitual use of morphine. But perhaps the simplest case of acquired toleration is observed in salmon and other fishes which live at one time in salt, and at another in fresh, water. If such a fish be transferred directly from sea water to river water, or *vice versa*, it would quickly die, the water to which it was unaccustomed at the time acting as a poison to it. But if the transition occur gradually, as it does in the migrations of the fish, where it passes from salt water to brackish, and then to fresh, or *vice versa*, the tissues of its body, and especially of its gills, become adapted to the gradual change, and no harm ensues. In the

ordinary course of the invasion of an organism by microbes the microbes appear to have the power of secreting some substance which will destroy the cells of the organism. If these are, however, protected against the poison by previous gradual inurement to its action, they resist the microbes and destroy them. The whole subject is still in its infancy, but the results already obtained raise great expectations for the future.

Duration of Immunity.

There is one point, however, which seems doubtful, and that is the duration of the immunity which may be thus conferred.

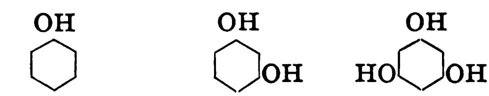
Sewill has found that by inoculation with small quantities of snake venom he can establish a certain tolerance for larger quantities of the poison injected at once; but this tolerance wears off after six months, so that it rather resembles the tolerance which is established for morphine by its continuous use than the immunity against small-pox which is conferred by vaccination. It is possible that the germs of a disease may establish in the cells of the organism which it attacks a power of producing some substance inimical to their growth, and that this power may continue for years unchanged without any external evidence of its presence. Possibly some evidence of such an alteration might be found by careful examination of the poisons excreted in the urine of an animal before and after preventive inoculation of anthrax, and careful comparison of the action of these substances upon the life of anthrax bacilli. But the whole question is a very wide one, and an enormous amount of patient and laborious investigation will be required before we get any accurate knowledge on the subject.

Chemical Structure as an Indication to the Choice of Antiseptics.

But there is one inquiry which is of still more immediate practical interest, and that is, What compound is likely to be most powerful as an antiseptic, and least likely to produce at the same time unpleasant or dangerous symptoms? Phenol itself has an antipyretic action, but its poisonous and antipyretic properties run too nearly parallel to allow of its being much used to reduce temperature.

Effect of Number of Hydroxyl Groups.

On comparing the action of phenol with similar compounds in which two or three atoms are replaced by hydroxyl, instead of one, as in phenol, it has been found that the toxic action is, upon the whole, rather increased with the increased number of hydroxyl groups, phenol being hardly so poisonous as resorcin, and this in its turn less poisonous than phloroglucin.



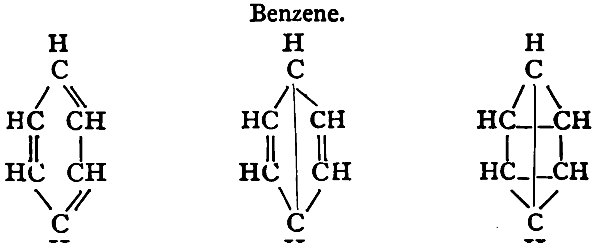
Phenol. Resorcin. Phloroglucin.

The rapidity of action of these drugs is in inverse ratio to their toxic power; phenol, which is least toxic, acts most quickly, and phloroglucin, which is most toxic, acts most slowly. Resorcin is apparently intermediate. This effect does not depend on their solubility in water, as phenol is the most sparingly soluble of the three.

Effect of the Position of Hydroxyl Groups.

But we have not merely to consider the number of hydroxyl groups in the body. We must consider also their position in relation to the benzene nucleus. This nucleus consists of six carbon atoms united together to form a closed ring. In benzene an atom of hydrogen is attached to each carbon, so that we have six hydrogen atoms attached to six carbons, and the formula is C_6H_6. It is not quite certain how the carbon atoms are united amongst themselves. According to Kekulé, they are alternately united by double and single affinities, while others have proposed connections between atoms on opposite sides of the ring.

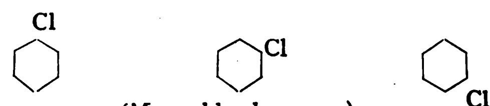
Benzene.



(Kekulé.) (Dewar.) (Ladenburg.)

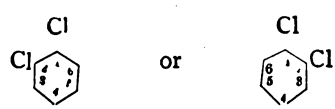
We must bear in mind that this ring is simply hypothetical, but it gives us a convenient means both of representing aromatic substances and of studying their relationship.

Whatever the real nature of the connection may be, it appears that the benzene nucleus is symmetrical; and that if we replace an atom of hydrogen in it by hydroxyl, chlorine, methyl, or any other radical, the product is the same whichever atom of hydrogen be replaced.



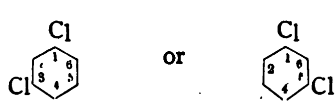
(Monochlor-benzene.)

But if we replace a second atom the case is different, for the fact that one atom in the original nucleus has been already replaced has rendered the nucleus unsymmetrical. If the second replacement occurs on a carbon atom next to the first it is represented in a formula by the figures 1 : 2, and is said to be in the ortho position.



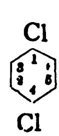
(Ortho-dichlor-benzene.)

If on the next atom but one it is represented in a formula by 1 : 3, and is said to be in the meta position.



(Meta-dichlor-benzene.)

And if in the next but two it is represented as 1 : 4, and is said to be in the para position.



(Para-dichlor-benzene.)

Effect of Position of Radicals on Chemical Behaviour.

The position of radicals replacing hydrogen in the benzene nucleus affects the chemical behaviour of the compound very considerably.

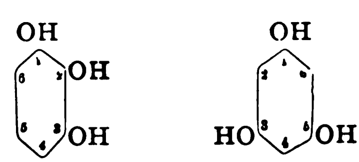
Thus if an alkyl, such as methyl, be attached to one carbon atom, the attachment of a second negative radical, such as hydroxyl, in the ortho position to the nucleus prevents its oxidation in acid solutions, but hastens it in alkaline ones, and there can be little doubt that the relative position of the radicals attached to the benzene nucleus will affect the processes of oxidation and reduction which it undergoes in the organism, as much as it would do in the hands of a chemist. We have, perhaps, too few data as yet to come to a definite conclusion regarding the exact alterations which the position of a group in the benzene nucleus will effect in its physiological action, but a number of most interesting data have already been obtained.

Dioxybenzenes.

Thus it has been found that in the case of the dioxybenzenes, where two hydroxyls occupy the ortho position, the action is most powerful. It is weakest in the meta position, and is intermediate in the para position in the benzene nucleus.

Trioxybenzenes.

In the case of the trioxybenzenes, where we have three hydroxyls, we find that when these are in the position, 1, 2, 3, or are consecutive, as it is termed, the toxic action is greater than when they are in the position 1, 3, 5. In the first instance, as in pyrogallol, any two hydroxyls are to each other in the ortho position, whereas in the second, phloroglucin, any two are in the meta position to each other.



Pyrogallol Phloroglucin

Replacement of Hydroxyl by Carboxyl.

If we replace the hydroxyl in phenol by carboxyl (COOH) we lessen its toxic power very considerably, though the substance we obtain—benzoic acid—still has considerable antiseptic power. If we replace one atom of hydrogen in the benzene nucleus by hydroxyl, and a second by carboxyl, we find that the same rule holds good as for the dioxy-compounds. Here, too, the rule regarding position holds good, for salicylic acid, in which the hydroxyl and carboxyl are in the ortho position, is more powerful than either of its congeners meta- and para-oxybenzoic acid, in which they are in the meta and para position respectively.

LECTURE III.

CONTROL AND CURE OF DISEASE.

We now pass from the prevention of disease to another subdivision of our subject. Antiseptics find their most important application in the prevention of disease. But many bodies belonging to this class have other actions which are extremely valuable in relation to the control and cure of disease. More especially is this true of their power to reduce temperature and relieve pain. We might therefore pass from antiseptics straight on to antipyretics. Or we might take another course, and on leaving antisepsis, one of the two greatest discoveries of modern therapeutics, we might turn to the other, viz., anæsthesia, and proceed to the consideration of anæsthetics. Both plans have advantages of their own. If we take anæsthetics first, it allows us to a certain extent to follow the subject of the relation between chemical structure and physiological action historically, and it has the further advantage of allowing us to begin with bodies of simple chemical structure and to proceed from them to the more complex. Such an arrangement would undoubtedly be best in a text-book, but as my object here is not to give you a full account of all that is known in relation to the connection between chemical structure and physiological action, but rather to point out its relations to the treatment and cure of disease, I shall take the other method and pass from antiseptics directly to antipyretics. There is a natural link between these two classes of remedies. Not only are antiseptic and antipyretic properties generally possessed by the same substances, but we use the same remedies to destroy microbes both outside and inside the body, and also to reduce the fever which the microbes cause after their entrance into the organism.

Besides this, a number of new facts have been ascertained regarding the functions of protoplasm by the use of bodies belonging to the aromatic series. I wish particularly to call your attention to those facts because they may help us to explain the action of other classes of drugs as well as that of antipyretics.

Movements of Cells.

On observing isolated cells, such as the leucocytes of the blood, we can see that they are endowed with life, and will continue to move about on the stage of the microscope as independent organisms for a considerable time after the death of the animal from which they have been taken. Their movements are of two kinds, viz., one of simple contraction or extension of the protoplasm in various directions, while the cell remains in its place, and secondly, movements from place to place. I call your attention specially to those kinds of movement because both are probably of practical importance. The movements from place to place enable the leucocytes, as was first observed by Addison and then by Waller, to move out of the blood-vessels. The importance of this diapedesis and of the further movements of the leucocyte amongst the cells of the tissues has been clearly demonstrated by Cohnheim and his followers; but it seems probable that movement of the protoplasm in a cell while it remains *in situ* may be no less important.

Respiration in Cells.

Kühne showed that isolated cells have the power of absorbing oxygen, by placing them under the microscope in water containing a little oxy-hæmoglobin. After a while. they absorbed the oxygen from the hæmoglobin and reduced it. This reduction was discovered by looking at the solution with the microspectroscope, and noticing that it gave the band of reduced hæmoglobin instead of oxy-hæmoglobin as at first. The experiments of Ludwig and his scholars upon circulation through single organs or parts of the body isolated from the rest, and also those of Pflüger and his school upon the gases of the blood, have shown that oxidation and reduction occur in the tissues, but that the

amount of each is not always the same, oxidation being sometimes predominant, and, at other times, reduction. Similar results have been obtained in living men by Pettenkofer and Voit. It was found by Harley that the absorption of oxygen and the elimination of carbonic acid by blood could be altered by admixture with various poisons. The power of quinine to lessen such processes was not only discovered by Binz, but brought by him into close relationship with the antipyretic power of the drug, and his researches formed a starting-point for numerous investigations into the action of antipyretics generally.

In the admirable lectures which he gave before this college last year, Dr. MacAlister gave such a complete account of the pathology of fever that I need not do more here than just recapitulate one or two of his chief conclusions.

Increased temperature may depend upon (*a*) lessened loss of heat by radiation or conduction, or (*b*) increased formation of heat by greater oxidation in the tissues, and especially in the glands and muscles. The oxidation by which heat is formed in these tissues is regulated by two or three nerve centres in the brain. Antipyretics, he informed us, appear to lessen oxidation within the body and diminish the formation of heat by stimulating these centres, but he did not discuss the mode in which stimulation of the thermal centres alters the processes of respiration in the tissues and thus lessens oxidation. This part of the question I propose to take up now, but before I can deal with the action of drugs as antipyretics I must ask your attention for a short time to some observations which have been made upon the respiratory functions of the cell.

Oxidation and Reduction.

From such experiments as those I have already mentioned, it has been known for some time that cells possess the power of taking oxygen from the air, from liquids containing it in solution, or from substances like hæmoglobin, which contain it in a loose state of combination. To this power of removing oxygen from other things the term "reducing" is given, while that of "oxidising" is applied to the power of giving off oxygen to other substances.

Double Action of Hæmoglobin.

Some bodies, like hæmoglobin, possess both powers to a large extent. A solution of hæmoglobin mixed with air absorbs the oxygen from it, and thus has a reducing action, but if this oxidised hæmoglobin be then mixed with some ferrous sulphate it gives up the oxygen to it, oxidises it, and forms ferric sulphate. It thus loses its oxygen and becomes reduced, the ferrous sulphate having acted upon it as a reducing agent.

Comparative Degrees of Affinity for Oxygen.

Substances differ in the degree of affinity which they have for oxygen, it being greater in some and less in others. Thus it happens that we might draw up a scale containing a number of bodies, each of which would have a greater affinity for oxygen than the one above and less than the one below it. Each one would therefore abstract oxygen from the one above it, and act as a reducing agent towards it, while it would give up oxygen to the one below it, and thus act as an oxidising agent.

EFFECTS OF REACTION AND ELECTRICITY ON OXIDATION AND REDUCTION.

Effect of Acid or Alkaline Reaction.

The degree of affinity for oxygen which many bodies possess is greatly altered by the reaction of the fluid in which they are dissolved, so that one which would have a powerful reducing action in an alkaline solution has none at all when it is acidulated.

Effect of Electric Currents.

Moreover, electric currents may originate processes of reduction or oxidation. Thus, if an electric current be passed through water, decomposition occurs, the hydrogen being liberated at the negative pole, and oxygen at the positive. If the electrodes are made, as they usually are, of a substance like platinum, with which the oxygen or hydrogen cannot combine, these gases are simply given off, but if the positive electrode is made of an oxidisable, and the negative one of a reducible substance, the oxygen and hydrogen will act upon them, and they will undergo reduction

or oxidation accordingly. By reversing the current, changes of the opposite nature will occur, oxidation giving place to reduction, and *vice versa.*

Formation of Urea.

By means of alternating currents of this sort Drechsel has succeeded in converting carbonate of ammonium into urea, and has rendered it probable that alternate oxidation and reduction are constantly occurring within the tissues of the living body.

Seat of Oxidation and Reduction in the Body.

The exact place where these processes occur and the exact manner in which they take place have still to be made out, but a great deal of information on these subjects has been obtained by Ehrlich in a most interesting and important research.

Oxidation and Reduction of Aniline Colours.

By the introduction of various aniline compounds into the circulation of living animals, either directly into the veins or indirectly by subcutaneous injection, Ehrlich has been able to show that constant processes of oxidation and reduction are going on throughout the animal body generally, but with very different intensity in the different organs and tissues.

Comparative Intensity of Respiratory Processes in Different Tissues.

In those whose functional activity is small, such as connective tissue, these processes go on slowly, but they go on rapidly in organs where the functional activity is great, as in the heart, the brain, and some of the unstriated and striated muscles.

Intensity of Reducing Power of Cells.

The power of the living cell to effect chemical changes in the substances which it absorbs is almost incredible, for alizarin blue, one of the substances which Ehrlich has employed, can only be reduced by the most powerful reagents outside the body, for example, by boiling with caustic potash and grape sugar, and yet it is completely reduced within the living body by the liver and

by the cortical substance of the kidney, and is rapidly reduced after death by the heart, liver, and muscular substance. When reduced it becomes white, but when oxidised it becomes blue, and thus the comparative amount of reduction in the tissues can be estimated by their colour.

Limits of the Reducing Power of the Tissues.

The alizarin blue is injected in the oxidised or blue state, and circulates in this condition in the blood, for the serum and also the fluid of the aqueous chamber of the eye have a distinct blue colour. Most of the organs of animals into which it has been injected have a blue colour, with the exception of those I have already mentioned. This shows that the reducing power necessary to change it from blue into white is greater than most of the tissues possess.

By using another pigment—indophenol blue, which is more easily reduced than alizarin blue—Ehrlich found that reduction occurred in almost all the tissues. It is evident, then, that, as very few tissues can reduce alizarin blue and almost all can reduce indophenol blue, the reducing power of the cells lies between the limits fixed by those two substances.

Tissues like a "Damped" Furnace.

The fact that the tissues possess this power of reduction shows that they are not saturated with oxygen, and yet they possess a sufficient amount of oxygen to enable them to carry on their functions. Their condition might be likened to that of a furnace where the entrance of air is so restricted as to allow sufficient but not too rapid combustion to occur, so that, if the ventilator were opened and more air allowed to enter the furnace, the fires would at once burn more hotly. In the case of the tissues of greatest functional activity, such as the heart and brain, the supply of oxygen must be very free, and that it is so is shown by the fact that they do not reduce alizarin blue during life, though they rapidly do so after death, and the brain will also do it during life if excited by electrical stimulation. In order to explain the processes of reduction and oxidation going on in cells, Ehrlich supposes that in the protoplasm we have certain chemical groups

which will take up oxygen readily, and will give it off to others with which it forms acid products.

Seat of Oxidation and Reduction in the Cell.

Respiratory Zones of the Cell.

In the living protoplasm he supposes there are three zones, the first having the greatest affinity for oxygen. This is usually saturated, and forms the reserve of oxygen for the use of the cell.

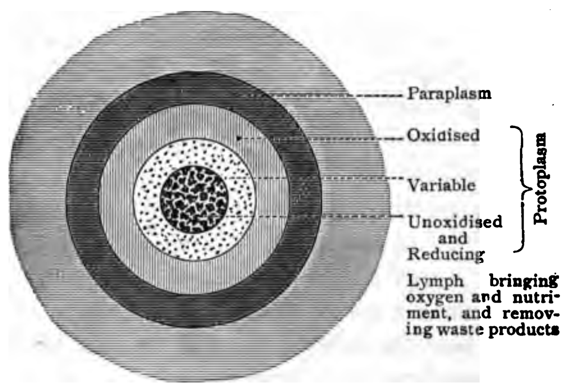


Fig. 19.
Diagram of a cell.

The second zone is that which is functionally active during the life of the cell, and it is sometimes reduced and sometimes oxidised. The third is always unoxidised, and is constantly exercising an attraction for the oxygen of the blood or lymph.

Alteration in Power of Reducing by Changes in Reaction.

It may well be supposed that the affinity of protoplasm for oxygen may be altered in a similar way to that of indophenol white, which, like protoplasm, is readily capable of undergoing alternate oxidation and reduction. In an alkaline solution the affinity of indophenol white for oxygen is very strong, and it readily becomes oxidised to indophenol blue by the oxygen of the air. But in a neutral solution its affinity for oxygen becomes slight, and in an acid solution is completely destroyed, so that in such a solution it no longer tends to attract oxygen, but on the

contrary gives it off readily, and consequently reducing agents quickly convert it into indophenol white. When the acid is neutralised and alkalinity restored, the attraction for oxygen is increased, and the oxidised blue product is again formed notwithstanding the continued presence of a reducing agent in the solution.

On again acidulating, reduction occurs, and the same cycle of changes between oxidation and reduction can be produced at will by mere changes in the reaction of the liquid, until the whole of the reducing substance is oxidised.

Effect of Functional Activity on the Reaction of Cells.

That similar changes of oxidation and reduction in the protoplasm of cells are largely influenced by their reaction has been found by Ehrlich to be the case, for by using another aniline colour which is a delicate reagent for acidity, along with indophenol blue, he noticed that reduction of the latter substance occurred, when indication of acid reaction was given by the former.

Regulation of Oxidation in the Cell.

The production of acidity, or rather, in most cases, the diminution of alkalinity in the protoplasm, lessens its affinity for oxygen, and thus the process of combustion in the cell is diminished or arrested by the formation of acid, though oxidation again begins as soon as the circulating blood or lymph has restored its alkaline reaction. The activity of the cell tends to generate acid products of tissue waste, and these will be formed all the more quickly the more actively the functions of the cell are going on. But their accumulation will tend to lessen the alkalinity of the cell, and consequently its affinity for oxygen. The processes of combustion will then diminish or stop entirely until the waste products have been removed. There is thus a sort of self-acting mechanism in the cell, which, to a certain extent, regulates oxidation within it. Yet this regulating arrangement, which might be likened to the appetite, which prevents reasonable people from eating too much, does not seem to be enough, for we find a further one, which actually prevents the oxygen from getting to the protoplasm,

and, with the few exceptions of the brain, heart, and some of the muscles, the tissues of the body are shown by their reducing power to have only a restricted supply of oxygen, or in other words, are burning like a furnace fire with partially closed dampers. Now the question arises, how is the supply of oxygen to the protoplasm restricted, and how is it that the supply may be, if necessary, increased? The damper which restrains combustion in the cell is, according to Ehrlich, the paraplasm, or cell juice which surrounds the protoplasm. This paraplasm presents considerable resistance to the diffusion of oxygen through it, and thus restricts the quantity which reaches the protoplasm.

Fig. 20.

Two pigment cells from the skin of a frog with the pigment granules fully diffused, so that the animal was of a black colour. The bodies of the cells are pale, containing chiefly colourless fluid, while some of the finest offsets are quite black, in consequence of the dark molecules being closely packed together in them. In the same figure a capillary fully distended with blood corpuscles is also given. After Lister.

Effect of Contraction of Protoplasm on its Respiratory Processes.

The amount of oxygen which will pass through the paraplasm

and combine with the protoplasm will vary according to the thickness of the paraplasm and to the area of surface of the protoplasm. When the protoplasm is contracted to its utmost extent, it will form a globe presenting a minimum surface to attract oxygen, and with a maximum thickness of paraplasm around it (fig. 20). When the protoplasm is extended it will present a maximum surface with a diminished thickness of paraplasm (fig. 21). It will therefore

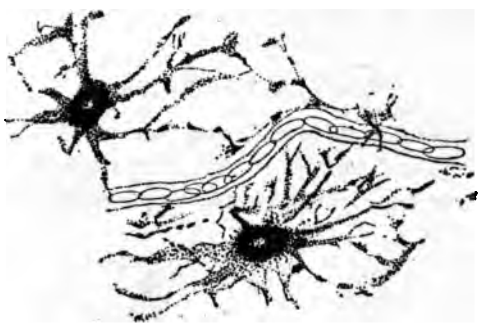


Fig. 21.

The colouring matter in the same cells as in Fig. 20 during the process of concentration. The dark molecules are already for the most part collected about the middle of the body of each cell, but in the very centre of each cell is a pale point, where the granules seem not yet to have insinuated themselves between the cell wall and the nucleus. The same capillary is seen much reduced in calibre. After Lister.

attract oxygen more readily, and combustion will go on more quickly within it.

Attempted Explanation of the Action of Antipyretics.

Let us now see if we can apply these data in explanation of the action of antipyretics.

In the Croonian Lectures last year Dr. MacAlister informed us that a number of antipyretics had been shown to affect the temperature of the body by acting upon definite centres in the brain; but he also told us that the chief seats of combustion in the body

by which temperature is maintained are the muscles and the glands. At present, so far as I know, we have no very satisfactory explanation of the mode in which these structures are affected by stimulation of the thermal centres. If we suppose, however, that stimulation of these centres causes contraction of the protoplasm in muscle and gland cells, so that its attracting surface to oxygen would be diminished, and the resistance to the passage to oxygen through the paraplasm increased in the way I have just described, we can see that oxidation would probably be greatly lessened and the temperature correspondingly reduced.

Binz's Work on Quinine.

The study of antipyretics received a great impetus, and, indeed, might almost be said to have started, from the work of Binz on quinine. From his experiments two very striking facts resulted.

Fig. 22.

The process of concentration is seen to be almost absolutely completed, the molecules being almost all of them aggregated into a black circular mass, occupying the middle of the body of the cell, the more circumferential parts of which contain only a colourless fluid, and are therefore invisible. After Lister.

The one was that quinine had the power to lower the temperature in febrile conditions which were not due to malaria; the other was that quinine had an extraordinary power of arresting the movements of leucocytes, causing them to draw in their pseudopods, and to contract into a sphere. In the case of free cells like the

white blood corpuscles we can see that such a contraction as this will considerably lessen the surface of protoplasm exposed to oxidation, but one can hardly see how the change of form is likely to interpose any obstacle between the oxygen contained in the serum surrounding the cell and the protoplasm. The case is different, however, if we take such a structure as the pigment cell of the frog. Here the protoplasm does not fill the whole cell equally at all times; occasionally it stretches itself out into all the ramifications of the branching cell, and then it will not only allow a large surface for oxidation, but will be separated by a comparatively thin layer of paraplasm from the lymph or interstitial fluid by which the cell is nourished (fig. 23). When the protoplasm contracts it forms a rounded mass in the centre of the cell, and then presents a minimum of surface for oxidation, and at the same time a maximum thickness of paraplasm is interposed between it and the cell wall

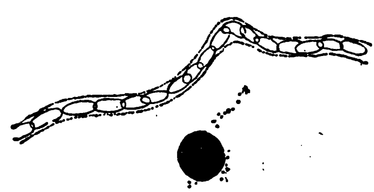


Fig. 23.

Shows the pigment in the lower of the two cells, concentration being still farther advanced. After Lister.

(fig. 22). If we suppose that quinine produces an effect upon the protoplasm of cells composing the tissues of the body similar to what it has upon leucocytes, we can at once see how it will lessen oxidation in the tissues, and thus act as an antipyretic. Nor is it necessary to assume that it exerts this effect directly upon the tissues themselves. The result will be the same if it stimulates thermo-centres in the brain and spinal cord, and causes contraction of the protoplasm through them. At the same time it is probable that quinine has an action on the tissues themselves, for Binz (Vorles-

ungen über Pharmacologie) has shown that the post-mortem production of heat is diminished in dogs that have been poisoned by quinine.

Why Antipyretics do not Reduce the Temperature in Health.

This hypothesis also enables us to explain the fact that antipyretics have comparatively little action upon the temperature of the healthy body, although they readily reduce the temperature in fever. For if the protoplasm in the cells of the healthy body be in a state of chronic contraction, so that its contour is not far removed from the sphere, a further stimulation to contraction will produce but little effect upon it. If, however, it be more diffused through the cell—as we might assume it would be in fever, and as Lister has shown it to be in inflammation*—the effect of causing it to contract would be very well marked both in regard to the change in its shape and the change in its respiratory function.

Relations of Physical and Vital Phenomena.

It seems almost ridiculous to speak of the colour of the skin on a frog's back in relation to the treatment of a patient suffering from fever, but Lister has discussed it in his paper on Inflammation, and Edward Jenner, the immortal discoverer of vaccination, noticed it in connection with the occurrence of rheumatism, as well as with the swelling of dry wood under the influence of an atmosphere loaded with moisture. His poem on the signs of rain is so good that I feel almost tempted to quote it in its entirety, but nevertheless I will restrict myself to quoting the lines directly bearing on this subject. He says—

"Hark! how the chairs and tables crack;
Old Betty's joints are on the rack;
The frog has lost his yellow vest,
And in a russet coat is drest."

The experiments of Lister and Brücke have shown that the darker colour is due to the extension of the protoplasm containing dark-coloured granules throughout the cell, while the yellow colour is simply due to the contraction of the protoplasm drawing the

* Joseph Lister, Phil. Trans., 1858, pp. 627-645.

granules together into one compact clump, and allowing the yellow colour of the cells below to appear. In some experiments made by Dr. Cash and myself on the action of various bodies belonging to the aromatic series, I was struck with the fact that in poisoning by some of them contraction of the pigment cells was a somewhat prominent feature.

Some other experiments by Mr. Bokenham and myself on antipyrin have given a contrary result, as the drug seemed rather to produce russet colour. On the other hand, knowing that iodoform had the power of stopping the movements of leucocytes, it occurred to me that it ought to have an antipyretic action, and, on looking up the subject, I found that it had. This subject is evidently one in which a very great deal more investigation is required before any conclusions can be arrived at. Yet I have thought it worth while to bring these facts and ideas before you, both because Ehrlich's observations seem to open out whole fields for investigation, and because the relationship which I have endeavoured to trace between them and the explanation of the action of drugs may render them more interesting to men engaged in the practical treatment of disease.*

ANÆSTHETICS.

I have already said that one of the greatest improvements in modern surgery is the introduction of anæsthetics.

Alcohol as an Anæsthetic.

The observation that pain can be abolished by alcohol is a very old one, for Solomon makes the drunkard say, "They have beaten me, and I felt it not," and apparently he determines to use it deliberately to prevent pain, for he says, "I will seek it [strong drink] yet again." The use of drugs to abolish pain in surgical operations has probably never been entirely forgotten, but their general and systematic employment only commenced with the use of nitrous oxide by Wells, in 1844, and of ether by his pupil Morton. Shortly afterwards a great number of substances were tried by

* Another interesting question might be to inquire whether any relationship exists between the power of aromatic substances to remove the russet colour from a frog's back and to cure the rheumatic pains which Jenner notices as indications of approaching rain.

Simpson, with the result that he chose chloroform as being the most convenient and safe. The power of producing anæsthesia, or perhaps I should say more definitely, the power not only to abolish pain and thus render an operation unfelt by the sufferer but to abolish reflex action, so that the surgeon may be able to operate more easily, is common to most of the substances of the fatty or alcoholic series. But it is greatly modified by two circumstances: (1) the position in the fatty or alcoholic group of the radical or alkyl which forms the basis of the substance; and (2) the nature of the element or radical with which the alkyl is combined.

Effect of Increase in the Number of Component Atoms in Bodies of the Alcohol Series.

It may be worth while to revert here to the illustration of a pocket knife which I used at an earlier part of these lectures. Let us imagine it tied to the end of a fishing rod. The fishing rod represents the radical, and the number of joints in it determines its position in the series. A single joint might represent methane, CH_3, and each additional joint might symbolize the addition of CH_2 to the radical. A single joint might be too short to reach as far as we wished, but each additional joint would increase not only the length but the weight of the rod, until it became too awkward to be useful or too cumbrous to be lifted at all. Now, something similar occurs with the members of the fatty alcoholic series. Every addition of carbon with hydrogen, CH_2, makes them heavier and more cumbrous. The members of the series beginning with methane, or marsh gas, which is a light gas, become gradually heavier and less volatile as the number of carbon atoms

$$
\begin{array}{ccc}
\begin{array}{c} H \\ | \\ H-C-H \\ | \\ H \end{array}
&
\begin{array}{c} H\ \ H \\ |\ \ \ | \\ H-C-C-H \\ |\ \ \ | \\ H\ \ H \end{array}
&
\begin{array}{c} H\ H\ H\ H\ H\ H\ H\ H\ H \\ |\ \ |\ \ |\ \ |\ \ |\ \ |\ \ |\ \ |\ \ | \\ H-C-C-C-C-C-C-C-C-C-H \\ |\ \ |\ \ |\ \ |\ \ |\ \ |\ \ |\ \ |\ \ | \\ H\ H\ H\ H\ H\ H\ H\ H\ H \end{array}
\\
\text{Methane (gas)} & \text{Ethane (gas)} & \text{Nonane (boiling point, 149·5°)}
\end{array}
$$

they contain increases. Petroleum ether, which is a mixture of pentane, C_5H_{12}, and hexane, C_6H_{14}, is a light, mobile fluid; higher members of the series form the soft paraffin or vaseline; while ose that are higher still form hard paraffin.

EFFECT OF THE STRUCTURE OF CARBON COMPOUNDS.

But the instrument consisting of a fishing rod and a pocket knife can be altered by changing the knife as well as by changing the number of joints in the rod. If in place of opening a gimlet point, which we may compare to hydrogen, I open a knife-blade, which we may compare to hydroxyl, I change the character of the instrument. If I open a blade at the end and one at the side I again alter its capacity for cutting, and if I replace the knife altogether by a dumb-bell, I may make the instrument into a club rather too heavy to wield.

Effect of Different Radicals or Alkyls.

Thus in the case of the alkyls their action differs according as they are combined with hydrogen in the hydrides, with hydroxyl, OH, in the alcohols, or with both oxygen and hydroxyl, as in the acids.

Moreover, both their physical condition and physiological action may be changed by replacing hydrogen by other elements. Thus, if we replace three atoms of hydrogen in marsh gas, CH_4, by chlorine, which has an atomic weight of 35·5, while that of hydrogen is only 1, we convert the light gas with a molecular weight of 16 into the heavy liquid, chloroform, with a molecular weight of 119·5. If in place of three atoms of chlorine we introduce three of iodine, each having a weight of 127, the molecular weight of the whole compound becomes 394, and in place of a permanent gas like marsh gas, or a heavy fluid like chloroform, we get a solid like iodoform.

The physical condition of the substance may be influenced by the number of atoms of other elements which combine with an alkyl as well as by their nature. Thus, when only one atom of hydrogen in methane, CH_4, is replaced by chlorine, the resulting monochlormethane, CH_3Cl, or methyl chloride, is a gas at ordinary temperatures, although it can be condensed by cold and pressure to a liquid which boils at 22°. Dichlormethane, or methylene chloride, CH_2Cl_2, is a heavy liquid boiling at 41°, and the trichlormethane, or chloroform, $CHCl_3$, is a still heavier liquid, which boils at 61°. It appears, then, that we can increase the atomic

weight of an anæsthetic and render it more solid by adding on carbon to the alkyl, or by replacing hydrogen with heavier atoms like chlorine or iodine. The more hydrogen atoms are thus replaced, the denser does the body become, so that it may pass from a gas to a liquid, and then to a solid at ordinary temperatures.

Effect of the Number and Weight of Atoms on Vapour Density.

If the temperature be raised sufficiently to convert it into vapour again, we can at once tell what the density of the vapour is, if we know the weight of the atoms composing the substance. Atoms, as I mentioned before, are incapable of independent existence, but unite with one another to form a molecule, which is the smallest quantity of any substance capable of independent existence. Now the volume which a molecule occupies is like the bed of Procrustes, and every molecule must fill it, however few or many atoms it may consist of, or however heavy or light these atoms may be. Thus the molecule of hydrogen consists of two atoms, and is written H_2. A molecule of chloroform, $CHCl_3$ contains five atoms, and one of ether, $(C_2H_5)_2O$, contains fifteen atoms. Yet the molecule of each body occupies the same volume, *i.e.*, 2 vols. The atom of hydrogen weighs less than any other, and its weight is taken as unity. The molecules contain two atoms, and so the molecular weight of hydrogen is 2. If the atoms in chloroform and ether had the same weight as those of hydrogen, their weight would be 5 and 15 respectively. But the atomic weight of carbon is 12, of oxygen 16, and of chlorine 35·5. Therefore the weight of a molecule of ether, $C_4H_{10}O$, is 74 $(12 \times 4) + (1 \times 10) + (16) = 74$, and that of chloroform, $CHCl_3$, is 119·5 $(12 \times 1) + (1 \times 1)\ (35{\cdot}5 \times 3) = 119{\cdot}5$.

As every molecule has the same volume, it is evident that the density of the vapour of ether is 74, and that of chloroform 119·5 as compared with 2, which is that of hydrogen.

This is usually known as Avogadro's law, and is commonly stated thus: Equal volumes of gas or vapours at like temperature and like pressure contain an equal number of molecules.

Effect of Alkyls on Nerve Centres.

It is probable, as I have said, that all the substances belonging

to the alcoholic series possess the power of abolishing to a greater or less extent the excitability of all the nerve centres within the body. They appear to act upon those centres in the inverse order of their development, destroying first the functional activity of the highest ideational and volitional centres in the cerebrum, those centres which are the latest to be developed, and which not only raise man above the animals, but raise individual men above their fellows. As their action increases, nerve centres of a lower development are affected or, as Hughlings Jackson puts it, the most highly organised centres are affected first, while the lowest, most simple, and at the same time most automatic and stable centres are affected last. The perceptive and motor ganglia, the reflex centres of the cord, the vasomotor and respiratory centres and the heart, all become paralysed when the action of the members of this group is pushed to its utmost extremity.

Different Action of the Members of the Alcoholic Group.

But they are not all rendered inactive in the same order by each member of the group. On this account some members are useful as hypnotics, simply inducing sleep as one of the first results of their action, although if the dose be large, the sleep may pass into complete unconsciousness or anæsthesia, with loss of reflex action. For the production of prolonged sleep we require a substance whose action will be slight, and at the same time prolonged. But for anæsthesia we require a substance which will act rapidly and powerfully, but will be quickly eliminated and cease to act very shortly after its administration is discontinued. We therefore look for hypnotics among the substances which have a heavy molecule, and are either liquid or solid in form, so that they may be given by the mouth, and being absorbed into the blood, continue to act for a length of time. We look for our anæsthetics amongst the lower members of the series which have a light molecular weight, and are either gases or volatile liquids. Although heavy liquids like paraldehyde, or solids like chloral hydrate, will act as anæsthetics when given in large doses, yet their use as such would be very dangerous, for the line between their anæsthetic action and their paralysing action

on the respiratory centre or heart is very narrow, and might easily be crossed by very slight excess in dose. The elimination of such substances being slow, we cannot at once get rid of their effects of excess in the same way as we can in the case of those which, like ether, enter the lungs as vapour, and are readily eliminated. It will, therefore, be convenient to consider the action of hypnotics and anæsthetics separately, although they may belong to the same chemical group.

Mode of Action of Anæsthetics and Hypnotics on Nervous Tissue.

But it may nevertheless be advisable to consider the mode in which they both act on nervous tissue at this time. We may divide the theories of action into three:

First, that they alter the *blood* in such a way as to render it incapable of maintaining the functional activity of the nerve-cells.

Secondly, that they alter the *circulation*.

Thirdly, that they affect the *nervous tissue* itself.

Some anæsthetics, such as nitrogen, nitrous oxide, and possibly marsh gas, and some of the other hydrides of the alcohol series, produce anæsthesia by a sort of process of suffocation, by excluding oxygen from the lungs, while the movements of respiration continue to go on. The reason for supposing that these substances simply act by exclusion of air is chiefly that in an animal breathing nitrous oxide anæsthesia comes on at the moment when the blood becomes quite venous;* and the anæsthesia does not come on when the nitrous oxide is sufficiently mixed with air. But for my own part I am inclined to believe that the nitrous oxid an action of its own on the nerve centres, and does exclude oxygen from the blood. For while we mi anæsthesia produced by this gas as s mply du cannot explain its curious stimulant on in it produces when mixed with air g those of suffocation.†

* Jolyet and Blanche, *Arch. de*

† Lauder Brunton, "Phar

"*Salt Frog.*"

The second theory that the anæsthetic action of drugs is due to their arresting or diminishing circulation in the nerve centres has been disproved in regard to the most important anæsthetics by a very simple experiment. When all the blood has been removed from a frog and its vessels have been washed out with a weak saline solution, it still remains active for a certain time; but if such a frog be placed in an atmosphere saturated with chloroform or ether, it becomes narcotised.

Effect of Circulation.

But while the action of anæsthetics cannot be wholly explained by exchanges in the circulation, they are very important, as we shall afterwards find, in regard to the action of hypnotics, and anæsthesia has actually been induced and operations performed by suddenly checking the circulation in the brain.*

Semi-coagulation.

We now come to the third theory—that anæsthetics affect the nervous tissue itself. The experiment already mentioned of anæsthetising a "salt frog" with chloroform shows conclusively that anæsthesia is due to the action of the chloroform on the brain.

The nature of this action has been supposed by Heinrich Ranke† to consist in a "transient fixation" of the albuminous molecules in the ganglion cells of the cerebral cortex, as well as in the nervous and muscular fibres. Claude Bernard and Binz have expressed similar views, and Bernard has used the term "semi-coagulation" to express the condition which occurs in the nerve cells, and probably this is nearly correct. The condition is, however, so transient that it might perhaps be better compared to the tetanic contraction of muscle, which quickly ceases when the irritant is taken away. In all probability the condition of anæsthesia and of tetanus are both to be regarded as the first stages of coagulation, and, if sufficiently prolonged, complete coagulation and death of the tissue will occur. A curious like-

* For examples *vide* Lauder Brunton, "Pharmacology," 3rd Edition, p. 205.

† H. Ranke, *Centralb.f.d. med. Wiss.*, 1877, p. 614; also 1867, No. 14.

ness, indeed, was found by Ranke between the action of anæsthetics on the brain and on the muscles; for they coagulate the albuminous substances extracted from both, and when injected into an artery they produce rigor mortis in the muscles it supplies.

Effect of Different Members of the Alcoholic Group upon Albuminous Substances.

In order to get a chemical basis for the action of alcoholic substances on nervous structures, it seemed to me advisable to ascertain the action of such substances on albuminous bodies. Dr. Sidney Martin and I have therefore commenced a research on this subject, and, although it is far from complete, we have already obtained the interesting result that while the lower alcohols—methyl, ethyl, and propyl alcohols—coagulate albumen almost completely, the butyl alcohols have less effect, and any precipitate they may produce is soluble, while the higher alcohols —amyl and heptyl—do not coagulate albumen at all.

Chemical Affinity between Narcotics and Nervous Tissues.

There can, I think, be little doubt that there is an affinity between many, perhaps all, the bodies belonging to the alcoholic series and the substances of which the nerve centres are composed. In all probability they enter into a loose combination with the nervous tissue for a time, and interfere with the processes of oxidation and reduction on which its activity depends. As Binz has well expressed it, morphine, chloral, ether, and chloroform possess a strong affinity for the substance of the cerebral cortex in man. This combines for a while with the hypnotics carried to it by the blood and by the resulting alteration in its tissue change, ("lessening of the dissociation of the living matter," in Pflüger's sense), it becomes unable to perform the functions of the waking conditions.

Contraction of Protoplasm in Nerve Cells.

But Binz has also noticed another condition, namely, that morphine produces in the cells of the nerve centres an alteration which reminded him of that caused by quinine in the white blood corpuscles. Referring again to Ehrlich's observation, we can see

that if anæsthetics and hypnotics cause contraction of the protoplasm in the cells of nervous centres they will thus lessen oxidation, and tend to diminish functional activity. Such a contraction might be caused not only by alkaloids like morphine, but by a mere change in the reaction of the cell or the fluid surrounding it. When free cells, such as amœbæ or infusoria, are treated with very weak acid they contract, and with weak alkali they swell up. It therefore seems probable that mere diminution of alkalinity by the products of the tissue waste may tend to lessen oxidation in the brain cells by contracting the protoplasm at the same time that the changed reaction lessens their affinity for oxygen.

Acids as Hypnotics.

The presence of any substance which will tend to increase the ormation of acid in the nerve cells ought, therefore, to have a hypnotic or even an anæsthetic action. Now, according to Binz, this actually occurs, and chlorine, bromine, iodine, ozone, and nitrites have all a more or less hypnotic action. The fumes of chlorine, bromine, or iodine inhaled by a frog cause paralysis of the nerve centres without any previous convulsions, and this paralysis is due to their action on the protoplasm of the nerve centres, according to Binz. On account of the local irritant effect upon the respiratory passages and the alteration they occasion in the blood they cannot be brought in contact with the nerve centres of mammals in the same way as with those of the frog, and therefore they cannot be employed as anæsthetics; but, nevertheless, they tend to exert a similar action in mammals, and when combined with alkyls they tend greatly to increase their anæsthetic action.

Action of Halogens on Muscle.

But I have already mentioned that the same process of contraction or partial coagulation which leads to anæsthesia occurs also, though to a much smaller extent, in the muscles, and the presence of any of the halogens, chlorine, bromine, or iodine appears to increase the effects of an alkyl upon the muscles even more than it does on the nerve centres.

Thus, the haloid compounds of the alkyls, although they are

more rapid anæsthetics, tend also to affect muscles, and more especially the heart, in a greater degree than those compounds from which they are absent. A similar tendency to paralyse muscular fibre, both in the limbs and the heart, was noticed by Cash and myself to be produced by compounds of the halogens, and particularly iodine and bromine, with ammonia or compound ammonias.*

Halogen Compounds as Anæsthetics.

The introduction of the halogens into anæsthetics, therefore, tends to increase the risk attending their use, but at the same time increases their anæsthetic power, and renders them more convenient. A knowledge of the chemical structure of an anæsthetic will thus give us a clue to its advantages and disadvantages, but only actual experiment can decide what its practical value will be.

Limitation in Choice of Anæsthetics.

But the application of any substance as an anæsthetic must not only be possible, it must be convenient and it must be safe. Thus, our choice of substances practically useful as anæsthetics from amongst the innumerable substances of the alcoholic group is limited.

Convenience.

In order to be convenient they must fulfil a good many requirements. They must be easily carried about, and must be readily applied without apparatus; they must not cause much struggling on the part of the patient; they should not take too long to produce anæsthesia, nor should the anæsthetic state last either too short or too long a time; they should not give rise to prolonged discomfort after their anæsthetic action has ceased.

Safety.

In order to be safe they should not have any marked tendency to paralyse the heart. All anæsthetics tend to paralyse the nervous system, beginning with the highest or most volitional centres in the cerebrum, and ending with the lowest or most automatic centres in the medulla oblongata. Hence, if they are pushed far enough, they will all paralyse the respiratory centre

* Lauder Brunton and Cash, Phil. Trans., 1884, 201 and 221.

and stop the respiratory movements; but these can readily be imitated artificially, and the blood can thus be kept aërated and the tissues supplied with oxygen until the anæsthetic has been either destroyed or sufficiently eliminated from the respiratory centre to allow it to regain its activity. The case is quite different when the heart stops; for then the supply of oxygen in the tissues entirely ceases. The anæsthetic is not eliminated nor destroyed, and the processes of life are arrested. Mechanical stimulation may help the heart to make a few feeble beats, and if artificial respiration be kept up actively so that blood charged with oxygen reaches the left ventricle, it may resume its activity. Nevertheless, stoppage of the heart is much more dangerous than stoppage of the respiration, and those anæsthetics which tend to enfeeble the heart are more dangerous than those which do not.

Inflammability.

In order to be safe in operations where a light is required, or where the actual cautery is to be used, the anæsthetic must not be too inflammable. This objection does not apply if there is no chance of the anæsthetic taking fire, but it may preclude the use, under certain circumstances, of an anæsthetic like ether, which might otherwise be suitable.

Bulk.

The gaseous form used to be very unsuitable for anæsthetics on account of the cumbrous apparatus required. Since the plan has been adopted of compressing gases into steel or iron bottles, the difficulty is much lessened, although not entirely got rid of, and nitrous oxide is constantly administered now, although it cannot be carried about so conveniently as ether or chloroform. Their gaseous nature was formerly a serious objection to the lower hydrocarbons of the alcohol series, methane, ethane, and propane, all of which are permanent gases, and to butane, which boils at 1°, and is thus a gas at ordinary temperatures. This objection would be obviated by using them in a compressed form like nitrous oxide.

Their inflammability, like that of ether, may preclude their use

under certain circumstances, and possibly the cold generated by their expansion may also prove an obstacle to their employment, yet it is possible that they might be usefully employed instead of nitrous oxide, along with ether, chloroform, or other anæsthetics higher in the series.

In 1849 Nunnely, of Leeds, in a letter to the *Lancet*, suggested the use of ordinary coal gas as a safe and convenient anæsthetic, notwithstanding its disagreeable smell. It has never come into general use, but it has quite recently been recommended as a sedative in whooping-cough.

Relation between Chemical Structure and Physiological Action of Anæsthetics.

The physiological action of carbon compounds was investigated by B. W. Richardson, in a most valuable and important research, in which he compared the action of higher and lower members in the alcoholic series, and examined the alteration produced in their action by the introduction of different radicals, such as chlorine, bromine, and iodine. This research was one of the first systematic attempts to connect chemical structure and physiological action, and forms the connecting link between the older researches of Simpson and others and the newer ones of Crum-Brown and Fraser.

As the results of his investigations he objects to gases on account of the difficulty of administering them, the short duration of their action, and the asphyxia they would produce if administered for a length of time; solids are impracticable, and the anæsthetic must therefore be fluid. The fluid should be homogeneous, as mixtures are unreliable; it should be stable, and not easily decomposed by heat or light; it should have a pleasant smell and cause no irritation when applied to the skin. The boiling point should not be too low, because fluids boiling under the temperature of the body must be used like gases to the exclusion of air, and those whose boiling point is too high remain long in the body, causing nausea and depression. These conclusions, although they seem *à priori* to be sound, have not quite been borne out by practical experience, for, according to them, chloro-

form is objectionable, as it irritates the skin, causes vomiting, and is too slowly eliminated. Ether also is objectionable, as having too low a boiling point, and requiring to be used like a gas to the exclusion of air. Nevertheless these two substances are practically the best anæsthetics we have got yet.

It may be well, in considering the directions in which we are to look for more perfect anæsthetics, to take up the members of different groups of bodies and consider their action.

Hydro-carbons.

We may begin with hydro-carbons or hydrides of the radicals, taking first those in which the carbon atoms are united by single linkage. The first four of these, methane, CH_4, ethane, C_2H_6, propane, C_3H_8, and butane, C_4H_{10}, have no action if inhaled along with plenty of air, but if inhaled pure they quickly cause anæsthesia, like nitrous oxide. Pentane, or amyl hydride, is one of the chief constituents of petroleum-ether. When inhaled it produces anæsthesia, passing off quickly, though not so quickly as that caused by methane,* and Richardson considers that it might be a useful anæsthetic. His conclusion in regard to the hydrides is that they acted practically by excluding air, so that anæsthesia by them is really due to suffocation, and says that, being "very stable as chemical compounds, practically insoluble in the blood, producing...no irritation, they inflict no injury on the living economy, unless they are inhaled in such quantities as to exclude air. Then they produce...a temporary insensibility, their power in this respect increasing with the increase of the carbon in the series; but owing to the insolubility of the agents in the blood the insensibility is in all cases of very brief duration, and would quickly be a fatal insensibility if by continuous administration it were prolonged."

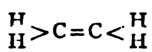
Octane, which is contained in petroleum, and along with heptane forms the commercial ligroine, produces anæsthesia like chloroform, but it is preceded by much excitement; there is also tendency to vomiting; so that it is practically of little use.†

Of the hydrides of the olefine or alkyline series, in which the

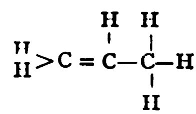
* Richardson, British Association Reports for 1889, p. 413.

† Versmann.

carbon atoms are united by two affinities, the one which should be first, methylene, C_2H_4, does not exist; and the next three, ethylene, C_2H_4,* propylene, C_3H_6, and butylene, C_4H_8, are gaseous



Ethylene.



Propylene.

at ordinary temperatures, and amylene C_5H_{10}, is a liquid with a disagreeable smell, which causes anæsthesia like chloroform, but is more dangerous to life.†

In acetylene, C_2H_2, the carbons are linked by three affinities ($H\text{-}C\equiv C\text{-}H$). When mixed with air in the proportion of 1 per cent. it causes deep narcosis in mammals, but this is always associated with symptoms of asphyxia and weakness of the heart.‡

Ethers—Formal—Acetal.

In ethers we have two alkyl or aromatic radicals united by oxygen. These may either be of the same kind, as methyl ether Me-O-Me, or of different kinds, as methyl ethyl ether, Me-O-Et, or methyl phenyl, Me-O-Ph. The former are called simple ethers, the latter mixed ethers. The examples I have given show that the radicals may either belong to the alcoholic or aromatic series. One might expect that the alcohols, which only differ from the hydrides by containing hydroxyl in place of hydrogen, would be more nearly allied than ethers to them, but this does not seem to be the case, and so I shall take the ethers next to the hydrides.

Methyl ether is a gas which, according to Richardson, acts like nitrous oxide, producing rapid and transient anæsthesia. When mixed with ethylic ether it produces easy anæsthesia, with no bad results. Ethylic ether is now so constantly used as an anæsthetic, I need say nothing at present about it.

* Ethylene mixed with about twice its volume of air narcotises rabbits in half an hour (Eulenburg, "Handbuch der Gewerbe Hygiene," 1876).

† Spiegelberg; Snow, *Medical Times and Gazette*, 1857, April 18th and August 8th.

‡ Lewin, "Toxicology," p. 184.

On the subject of the action of mixed ethers we possess little information, and probably researches in this direction might be made with advantage.

Methylene dimethyl ether, $CH_2<\begin{smallmatrix}OCH_3\\OCH_3\end{smallmatrix}$, usually known as methylal or formal, according to Richardson* produces anæsthesia slowly, but its action is deep and prolonged. Ethylidene-diethylether, or acetal, $CH_3CH<\begin{smallmatrix}OC_2H_5\\OC_2H_5\end{smallmatrix}$, also acts as an anæsthetic, but causes congestion of the head, sickness, and vomiting.†

Esters.

In ethers we have two positive radicals united by oxygen, but in esters we have one positive and one negative united in this way. Esters are indeed salts of organic radicals corresponding to salts of the alkalies. Several of them have been tried as anæsthetics. Amongst these are formate of ethyl and the acetates of methyl, ethyl, isopropyl and propyl, butyl, and amyl. Formate of ethyl is irritating to the throat and air passages. It causes muscular excitement, tends to cause vomiting, and produces stupor but not actual sleep. Acetate of methyl produces deep stupor without muscular excitement, but its anæsthetic action is not certain. Acetate of ethyl produces anæsthesia like ether, but acts more slowly. The acetates of the higher members of the series appear to have a slower and more prolonged action, and to produce much exhaustion.

Alcohols.

Although these may cause anæsthesia when given internally, or even when their vapour is very freely administered, yet they are not suitable as anæsthetics. According to Dr. Richardson ‡ the first published case of surgical operation under anæsthetics was performed in 1839 by Dr. Collier, on a person who was rendered insensible by breathing the fumes of alcohol, but such anæsthesia is too slow and too prolonged.

* Richardson, Brit. Ass. Reports for 1868, p. 184.
† Rabuteau, *Gaz. Méd. de Paris*, 1879.
‡ Richardson, Brit. Ass. Reports, 1869, p. 417.

Aldehydes.

These are too irritating, when applied externally, to be used as anæsthetics, but we shall have to consider their internal use as soporifics afterwards.

Acids.

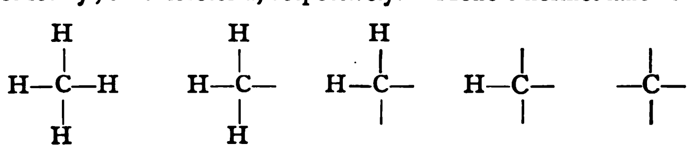
The same remark applies to acids as to aldehydes.

Haloid Compounds of the Alkyls.

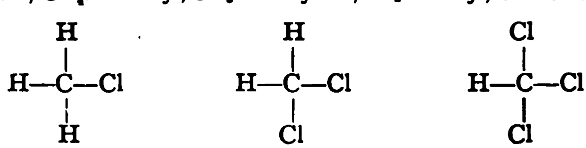
The compounds of alkyls with chlorine and bromine form useful anæsthetics. Those with iodine are denser and less applicable.

Compounds of Methane and Chlorine.

There are three compounds in which the hydrogen of methane is replaced by chlorine which have been used in medicine. The nomenclature of these substances and their relation to one another are simple enough if we term them mono-, di-, and tri-chlormethane, but if we speak of them in relation to the alkyl or hydro-carbon radical to which the atoms of chlorine are united, the relationship is confused by the fact that the introduction of each chlorine atom displaces an atom of hydrogen and thus alters the radical. We are thus obliged to speak of the three substances as chloride of methyl, bi-chloride of methylene, and tri-chloride of formyl, or chloroform, respectively. Mono-chlormethane is a



Methane, CH_4. Methyl, $\overset{\mathrm{I}}{CH_3}$. Methylene, $\overset{\mathrm{II}}{CH_2}$. Formyl, $\overset{\mathrm{III}}{CH}$. Carbon, $\overset{\mathrm{IV}}{C}$.



Monochlormethane, CH_3Cl, or Methyl-chloride. Dichlormethane, CH_2Cl_2, or Methylene bichloride. Trichlormethane, $CHCl_3$, or Formyl tri-chloride, or Chloroform

gas which is soluble in ether, and Richardson recommended this

solution as an excellent anæsthetic. The gas was used in dentistry with good results. Eulenberg found that it caused much local irritation, but the symptoms he observed lead one to suspect that the gas he used was impure. Di-chlormethane or bi-chloride of methylene has been the subject of much dispute, and it is very uncertain how far it has ever been used as an anæsthetic, for some of the preparations supplied under its name have consisted of mixtures of chloroform and alcohol. The experiments of a recent observer who claims to have used a pure substance appear to confirm the statements originally made by Richardson. The amount of labour which has been wasted upon experiments with substances bearing false names, and purporting to be what they were not, shows the necessity for the co-operation of pharmacological experiments and scientific chemists, and we may, perhaps, hope that if any pharmacological research is ever carried out under the auspices of this College, it may either be done with the aid of a chemical department in the College itself or in conjunction with such a research laboratory as has lately been instituted by the Pharmaceutical Society.

Chloroform.—Chloroform still remains one of the best of our anæsthetics notwithstanding the fact that it paralyses the heart much more readily than ether.

When the last atom of hydrogen in methane is replaced by chlorine all relationship to methane is lost, and the compound becomes tetra-chloride of carbon. This substance acts like chloroform, but more slowly and more persistently; it also tends still more to depress the heart.

Compounds of Ethane and Chlorine.

Let us now pass to the compounds of ethane. Mono-chlor-ethane (chloride of ethyl), is a fluid boiling at 12°. It was one of the earliest substances used as an anæsthetic, as it was tested in surgical operations by Heyfelder in 1847. He found that it acted more quickly than ether, and its effects passed off more quickly.

Trichlorethane, or methyl chloroform (CH_3,CCl_3), was said by Rabuteau to be unsuitable as an anæsthetic, but Dubois and

Roux* have found it, they say, to be even better than chloroform.

Other Chlorine Compounds.

Ethylene chloride, or Dutch liquid, was first recommended by Nunnely, but was afterwards allowed by him to have no advantage over chloroform. It causes irritation of the respiratory passages, vomiting, and prolonged languor and discomfort afterwards, and even opacity of the cornea. †

Ethylidene chloride, in the cases where it has been tried, appears to have acted well, but a fatal case soon after its introduction caused its use to be discontinued.

Mono-chlor-ethylidene chloride, or methyl chloroform, acts as a good anæsthetic upon frogs and rabbits, causes excitement in dogs, but acts as a rapid anæsthetic in man, leaving no discomfort behind. Its preparation is difficult and expensive, and experiments with it are few.

Mono-chlor-ethylene chloride produces in man anæsthesia in about fifteen to eighteen minutes; quickens the pulse, instead of slowing it like chloroform; in its general action it seems more to resemble ether than chloroform, and, like ether, it produces flushing of the face and salivation.

Tetra-chlor-ethylene causes anæsthesia, but irritates the bronchial tubes; and perchlor-ethane is a rapid anæsthetic, but tends to kill quickly by producing cerebral hæmorrhage.

Iodine and Bromide Compounds.

Amyl iodide causes anæsthesia, which comes on slowly and lasts a long time.

Bromoform, $CH\ Br_3$, corresponds exactly to chloroform in its chemical constitution, and was therefore early recommended as an anæsthetic.‡ Its action is very much like that of chloroform, but is said to be very uncertain and transient,§ so that it can only be used for short operations.‖ This seems doubtful, as its boiling point is 152° C., while that of chloroform is 61° C.

* *Compt. rend.*, 1877, p. 1549.

† Dubois and Roux, *Compt. rend.*, 1887, t. civ., p. 1869.

‡ "Handb. bd. Gewerbe Hygiene," 1876; *Gaz. Med. de Paris*, 1877.

§ Rabuteau, *Gaz. Hebd. de Med.*, 1869.

‖ Eulenberg.

Bromide of ethyl, C_2H_5Br, is a powerful anæsthetic. It was recommended by Nunnely,* in 1849, but fell into disuse. It was again revived about ten years ago,† but it tends to cause irritation of the respiratory passages, and is also liable to decomposition with evolution of bromine. ‡

Ethylene bromide, $C_2H_4Br_2$, appears to have but slight power as an anæsthetic, and tends to cause paralysis of the extremities and stoppage of the heart. § It appears to have a particular action upon the respiratory centre, greatly diminishing the desire to breathe, || and possibly it might be used with advantage in asthma and violent cough.

On account of its solid form, iodoform is unsuitable as an anæsthetic. Iodide of ethyl, C_2H_5I, is a liquid, boiling at 71°. It acts like chloroform and bromide of ethyl as an anæsthetic, but the anæsthesia is longer in coming on and is more permanent. At present it is only employed to relieve spasm of the respiratory passages, but for that purpose it is exceedingly useful.

Ethylene iodide, CH_2ICH_2I. is a crystalline substance, subliming at 100°. Its fumes produce anæsthesia, but it causes much irritation¶ of the respiratory passage and death by asphyxia.**

From the short *résumé* I have given of the action of substances which have been tried as anæsthetics, it is evident that notwithstanding the importance of the subject, there is still much information to be desired and much need for further investigation. More especially is this to be desired in regard to mixed ethers and their chlorinated compounds.

Hypnotics.

We may now pass from the subject of anæsthetics to that of soporifics and hypnotics. These are substances which merely cause natural sleep, from which the person can readily be awaked by external stimuli, instead of producing complete unconscious-

* Nunnely, Trans. of Prov. Med. and Surg. Assoc., 1849.
† Turnbull, "Manual of Anæsthetics," Lewis, London, 1880.
‡ Richardson, *Med. Times and Gaz.*, 1871. § Rabuteau.
|| Rabuteau, *op. cit.* ¶ Rabuteau, *Gaz. Med. de Paris*, 1878.
** Eulenberg, "Hand. bd. Gewerbe Hygiene," 1876.

ness, in which the most powerful stimuli are absolutely unfelt. As I have already mentioned, many substances produce sleep in the earlier stages of their action, and anæsthesia when their action is pushed to a further extent. But there are also some drugs which tend to produce sleep, but will hardly act as anæsthetics. Before we pass to the drugs which are used as soporifics, it will be almost necessary for us to consider shortly the physiology of sleep.

Physiology of Sleep.

In healthy sleep the person becomes unconscious of the external world, voluntary action ceases, and even the automatic centres for the respiration and circulation act less energetically, so that the breathing becomes slow, the pulse quiet, and the vessels tend to dilate. This dilatation of the vessels may be so well marked that it causes the feet to swell, and renders a pair of well-fitting boots too tight. At the same time it makes one more liable to be chilled by exposure to external cold while asleep than while awake. This condition of the vessels has been regarded by some as the cause of sleep rather than its consequence, for the two principal theories to explain sleep are, first, that it depends upon anæmia of the brain; and secondly, that it is due to an exhausted or inactive condition of the brain-cells.

Condition of the Nerve Cells.

In all probability the truth is that sleep depends upon the condition of the brain-cells, but this is so much influenced by the circulation that frequently the condition of sleeping or waking will depend entirely upon the cerebral circulation. We shall understand this more easily by referring again to Ehrlich's experiments upon oxidation and reduction in the tissues. You will remember that the grey substance of the brain is possessed of a great power of reduction, as shown by the readiness with which it reduces aniline colours after death, but during life the necessity for oxygen is so great that it retains within it a sufficient quantity of stored up oxygen to prevent such reduction taking place under ordinary circumstances. But if its functional activity be augmented by stimulation its store of oxygen is used

up, and thus it becomes ready at once to reduce. Its very activity, however, gives rise to the formation of acid products which lessen its reducing power, so that the mere supply of fresh oxygen would not be sufficient to restore it to its previous condition unless the acid were neutralised.

Effect of Arterial Blood.

Arterial blood supplies both these requirements by neutralising the acid, as well as supplying oxygen to the brain-cells. Thus, in some conditions of the brain simple increase in the supply of arterial blood will restore functional activity and cause wakefulness, while diminished supply will produce sleep.

Effect of Position.

This has been beautifully shown by Friedländer in a research on the hypnotic properties of isopropyl alcohol. Here the condition of sleeping or waking was simply determined by the position of the animal. If it were held up by the legs so as to increase the supply of blood to the head, it at once awoke, but when held up by the ears it immediately fell asleep. By alternating the positions sleeping and waking could be induced at will.

We see the same effect of the circulation in man, more especially in debilitated subjects; for some people with feeble tension tend to fall asleep even while standing up, and do so at once on sitting down, and yet are very wakeful in the horizontal position.

Effect of Food.

We very frequently find that people tend to fall asleep after a hearty meal. It is possible that this may be partly due to the absorption of certain digestive products, which may act as soporifics, but it is probable that the dilatation of the gastric and intestinal vessels which occurs during digestion has much to do with the production of sleep, by drawing away blood from the brain.

Effect of Cold.

We know, too, that cold, unless very intense, tends to prevent sleep, and we see that it also causes contraction of the superficial

vessels. It seems probable, therefore, that it prevents sleep in a great measure by driving the blood from the surface of the body to the brain. We cannot see the intestinal vessels, but we know that the abdominal walls are thin in front; and it is almost certain that external cold will act through the abdominal walls on the intestinal vessels, and cause them to contract likewise. Such contraction will also drive the blood to the brain, and tend to prevent sleep, but warmth to the abdomen will tend to relax them and induce sleep. This is probably the reason why dogs, before going to sleep, curl themselves up, so that their abdomen is kept warm by their limbs, and men do the same thing when exposed to external cold.*

Effect of High Tension.

In cases where the blood tension is high, as in chronic Bright's disease, we often find troublesome insomnia, whereas in cases of debility with low tension we often find troublesome drowsiness. The condition of the circulation is, therefore, a most important factor in the production of sleep, but it will by itself no more explain completely the insensibility of sleep than it will that of anæsthesia.

Action of the Products of Tissue Waste on the Brain.

We must now turn to the condition of the brain-cells themselves. As Ehrlich has shown, the acid products of their functional activity tend to lessen their reducing power, or, in other words, their power of absorbing oxygen. But it is highly probable that other products of tissue change, either in the brain itself or in the rest of the body, have a similar power to that of acids upon the brain cells.

Products of Tissue Waste by Day and by Night.

At all events, Bouchard has found that the toxic substances excreted in the urine during the day have a soporific action, while those excreted during the night have a stimulating action.

* Rosenthal, *Berlin Klin Woch.*, 1872, No. 38.

Self-regulating Mechanism of Sleeping and Waking.

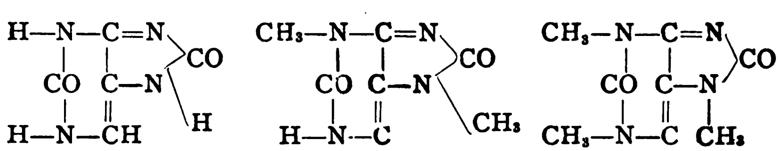
It would thus appear that there is a sort of self-regulating mechanism in the body, by which sleeping and waking are made to alternate. During the waking hours soporific products are formed, and these, gradually accumulating, will by-and-by induce sleep, while during sleep stimulating products are formed which, after a certain number of hours, will stimulate the brain to wakefulness.

Voit's Observations.

Now Voit found that during the waking hours more carbonic acid is given off, while during sleep the reverse is the case, and more oxygen is absorbed than carbonic acid eliminated. It is therefore evident that during waking, the organism as a whole is an oxidising agent, while during sleep it is acting as a reducing agent.

Nature of Leucomaines formed during Sleep and Waking.

We might therefore expect the products of the waking hours, those products which have a soporific action, to be more highly oxidised, while those of sleep, which have a stimulating action, would be rather products of reduction. The chemical constitution of these products still requires investigation, but we know that amongst the substances resulting from tissue waste there is a group of bodies closely allied to urea and uric acid. Amongst these is xanthine, the chemical constitution of which will appear from the graphic formula.



Xanthine. Theobromine. Caffeine.

Relationship of Tea, Coffee, and Cocoa to Products of Tissue Waste.

Xanthine is closely allied to theobromine and caffeine, the active principles of cocoa and of tea or coffee respectively, for the former

is dimethyl, and the latter is trimethyl xanthine. The stimulating effect upon the brain of cocoa, and to a still greater degree of tea and coffee, is universally known. This stimulating action would lead us to regard them as belonging to the class of products formed during sleep. During the waking hours we might reasonably expect that the substances formed, at least in the early part of the day, would have no narcotic action, even although they should be products of oxidation, but as the day went on the products of waste might gradually assume a more and more soporific character, until in the evening they again produced sleep. If this were so, we might naturally expect that by oxidation of some of the stimulant substances I have mentioned we might get products having no very marked physiological action, and others having a narcotic action.

Production of Narcotics from Stimulants.

This is the case, at least with caffeine, for while hydroxy-caffeine* has still a stimulating action, it is less powerful than caffeine; caffeine-methyl-hydroxide † seems to have neither stimulating nor soporific action, but ethoxy-caffeine ‡ acts as a soporific instead of a cerebral stimulant like caffeine itself.

Subdivision of Hypnotics.

It will be noticed that in the last-mentioned substance, ethoxy-caffeine, we have a compound of a radical, belonging to the alcoholic series, with one in which ammonia plays a prominent part. These two constituents are examples of two classes of soporifics, and a convenient subdivision of the classes is into—

(1) Substances belonging to the alcoholic group; and

(2) Substances allied to urea or uric acid.

CHANGES IN THE BRAIN-CELLS DURING SLEEP.

Let us now turn from the products of tissue waste which may act upon the brain, to consider what changes the brain-

* Filehne, *Arch. f. Anat. u. Physiol.*, 1886; *Phys. Abt.*, p. 72.

† Schilling, *Ztschr. f. Naturwiss*, 1884, Bd. 57, p. 207.

‡ Filehne *op. cit.*; Dujardin-Beaumetz, *Bull. gen. de Thérap*, 1886, 241.

cells undergo during sleep. I have already entered so fully into the subject, when speaking of anæsthetics, that all I need do now is simply to remind you that hypnotics may probably lessen the functional activity of the cerebral cells (1) by causing their protoplasm to contract, and thus interposing a barrier of paraplasm between it and the oxygen brought by the blood, and (2) by lessening the affinity of the cells for oxygen by diminishing their alkalinity, or by entering into actual combination with them for a time, and thus altering their chemical relationships. The products of tissue waste in the brain cells appear to be of acid nature and therefore lessen oxidation. But as Preyer has suggested, lactic acid is a product of muscular waste, and if much of it be formed in consequence of violent or prolonged exertion, it will pass into the circulation and tend to lessen the alkalinity of the brain as well as other tissues. Sleep might therefore be induced by a long walk, where acid is formed in the limbs, as well as by prolonged mental work, where the acid is a product of the brain itself.

Carbonic Acid and Deficient Oxygen.

One of the final products of tissue waste is carbonic acid, and this likewise has a soporific and anæsthetic action. One is usually accustomed to associate carbonic acid poisoning with convulsions; but from careful researches on this point, it would appear that these are not due to the presence of carbonic acid but to the absence of oxygen. It would thus seem that deficient oxidation in cases of suffocation produces in a few minutes intense stimulation of the nerve centres, while the lessened oxidation occurring in sleep has a similar but much slighter effect in the course of several hours. It is probable that in both cases the stimulation which gives rise in the one case to waking and in the other to convulsions is immediately caused by products of tissue waste.

Close Rooms: Sleeping in Church.

The drowsiness which comes on in a confined atmosphere is probably of complex origin, and while external warmth may assist it and carbonic acid also be an important factor in its pro-

duction, it is not unlikely that volatile poisons excreted from the lungs and skin may help to cause it. Carbonic acid in the cells of the cerebral cortex may, like other acids, lessen their affinity for oxygen, and thus by itself diminish their functional activity. But it may have a still more powerful action indirectly if certain substances are present in the blood, and more especially organic compounds containing chlorine, bromine, or iodine; for it may decompose these compounds and liberate hydrochloric, hydrobromic, or hydriodic acids within the nerve tissue itself. These will exert a much more powerful action than the carbonic acid. It is probable that some decomposition occurs when the sodium salts of an organic acid are introduced into the circulation, and thus sodium lactate may have a soporific action as well as lactic acid itself. Sodium propionate, butyrate, and valerianate have also a narcotic action, increasing in strength with the rising number of carbon atoms contained in each.*

Bodies of the Alcoholic Series as Hypnotics.

Alcohols.

In discussing this part of the subject I must refer to the tables (Appendix) for the chemical structure of the bodies I mention.

The action of alcohol as a soporific is widely known, and the practice of taking a glass of hot water and spirits as a "nightcap" is far from uncommon. The success of this plan would naturally lead one to look amongst the alcohols in the higher series for some substance which would be still more powerful, and might be given in smaller doses. The narcotic power of the alcohols increases as we ascend in the series, and the sopor induced by them is also of longer continuance. There is only one methylic and ethylic alcohol, but there are two propylic, four butylic, and eight amylic. The number of possible isomeric alcohols having the same chemical composition, though differing in constitution, increases rapidly as we ascend in the series. There are three divisions of alcohols, namely, (1) primary, (2)

* H. Mayer, *Arch. f. exp. Path. u. Pharm.*, Bd. xxi., p. 137.

secondary, and (3) tertiary, according as the carbon atom to which the hydroxyl is attached is united to one, two, or three radicals (*vide* Appendix).

Amylene Hydrate.

Tertiary amyl alcohol, or, as it is often called, amylene hydrate, was recommended by Schmiedeberg* as a hypnotic, and it has lately been introduced into practice by Von Mering. It is said to be intermediate between chloral and paraldehyde, safer than either, and not likely to disturb the digestion. When we consider that the next number of the series above amyl, namely, hexyl, may yield thirty-eight alcohols, and that thirteen of those are actually known, we can readily see what a possible field there is for the introduction of new hypnotics.

ETHERS AS HYPNOTICS.

Methylal.

The ethers are as a rule very volatile, and are more used as anæsthetics than hypnotics. One of them, methylene-di-methyl-ether, or methylal or formal, ${H \atop H}>C<{OCH_3 \atop OCH_3}$, has recently been recommended as a soporific. Its rapid elimination, however, renders it somewhat unsuitable, and in addition to this, patients appear to become very quickly accustomed to its use, so that the dose has to be constantly increased.

Sulphonal.

The chemical name of this substance is diethyl-sulphon-dimethyl-methane. This long name shows that it consists of methane, or marsh gas, ${H \atop H}>C<{H \atop H}$ or CH_4, in which two atoms of hydrogen are replaced by methyl, CH_3, thus: ${H \atop H}>C<{CH_3 \atop CH_3}$. But this is not all, for this body only corresponds to the last half of

* Schmiedeberg, *Practitioner*, December, 1885, p. 419.

the name, and is dimethyl-methane. It resembles methylal to a certain extent, only the two methyl groups are connected directly with the carbon of the original methane instead of the connection being effected by means of oxygen as in methylal. In order to complete the structure of sulphonal we must replace the other two atoms of hydrogen by ethyl; but if these were connected directly to the carbon in the same way as the two methyls are, we should get diethyl-dimethyl-methane $\frac{C_2H_5}{C_2H_5}>C<\frac{CH_3}{CH_3}$. But in sulphonal the connection of the two ethyls is effected by the SO_2 group, which plays a part like that of O in methylal in connecting alkyls with the carbon. We thus get:

$$\begin{matrix} C_2H_5SO_2 \\ C_2H_5SO_2 \end{matrix}>C<\begin{matrix} CH_3 \\ CH_3 \end{matrix}$$

Diethyl-sulphon-dimethyl-methane
or Sulphonal.

This appears to be one of the most effective of all the newly introduced hypnotics, and although it does not, like morphine, compel sleep, it induces sleep in a pleasant manner, and has few disagreeable after effects and little or no danger.

ALDEHYDES* AS HYPNOTICS.

Paraldehyde.

Aldehydes have a strongly irritant action upon mucous membranes, and this is a great objection to their use as hypnotics. But they have a power of uniting with themselves, or polymerising as it is termed, and these polymeric forms are less irritant. Ethylic aldehyde unites with itself, and when three molecules of it combine it forms paraldehyde. When several molecules, the number of which is unknown, combine, it forms metaldehyde. Paraldehyde is a useful hypnotic, which does not depress the action of the heart like chloral, and does not give rise to discomfort next day. The chief objection to it is its unpleasant smell, which it imparts to the breath and which hangs about the patient for very many hours.

* *Vide* Appendix.

Haloid Derivatives of Aldehyde.

Chloral—Bromal—Iodal.

The substitution of a halogen for hydrogen in an aldehyde greatly increases its narcotic power, and tri-chloraldehyde, or chloral, as it is usually termed for the sake of brevity, is one of our best hypnotics.

The introduction of this drug into medical practice we owe to Oscar Liebreich, and it is one of the first-fruits of the rich harvest of practical benefit to mankind which is now beginning to be gathered from investigations into the relationship between chemical structure and physiological action.

Chloral itself is an oily liquid, and it is not chloral itself, but the compound which it forms with water, chloral-hydrate, which is employed in medicine. The relationship of these substances to aldehyde on the one hand and to bromal and iodal on the other will readily be seen from the following formulæ :

Aldehyde $CH_3.CHO$
Chloral $CCl_3.CHO$
Chloral-hydrate $CCl_3.CH(OH)_2$
Bromal-hydrate $CBr_3.CH(OH)_2$
Iodaldehyde $CH_2I.CHO$
Butyl-chloral-hydrate $C_4H_5.CH(OH_2)$

From the soporific effect of bromides one would have expected bromal to be a more powerful soporific than chloral, but other actions which it exerts on the body appear to interfere with its action on the nerve centres. In animals it causes much irritation of the respiratory passages, and in large doses dyspnœa and cyanosis. First excitement is observed, but this may be due to the interference with respiration, and not to the action of the drug on the brain. Large doses produce anæsthesia, but do not cause much somnolence. The replacement of hydrogen by iodine appears to increase the action of the drug upon peripheral nerve centres or muscles.* This action of iodine appears in its compounds with ammonia and

* Brunton and Cash, *Phil. Trans.*, 1884, Pt. I, pp. 199, 201, and 219.

compound ammonias, and it occurs also in its combination with aldehyde. Iodaldehyde, in which only one atom of hydrogen instead of three is replaced by iodine, has by no means such a powerful hypnotic action as chloral, and it has a powerfully depressing action on the heart.*

The difference between chloral and the substances just mentioned consists in the nature of the body replacing the hydrogen in aldehyde. In butyl-chloral the substitution by means of chlorine is exactly the same as in chloral, but it occurs in an aldehyde (butyl-aldehyde) higher up in the alcoholic series than the ordinary ethyl-aldehyde or acetic aldehyde, which forms the basis of chloral. Butyl-chloral is much less soluble than chloral is; this relative insolubility is probably due to its higher position in the alcoholic series, for the same diminution of solubility as we ascend in the series has been noticed by Schmiedeberg in the case of urethanes. It is a less powerful hypnotic than chloral, and appears to have an anæsthetic action on the cerebral nerves, but it is not easy at present to show what relationship these properties bear to its chemical structure.

Ketones† as Hypnotics.

Hypnone.

In aldehyde we have the group CO, attached on the one side to a radical, and on the other to hydrogen; in ketones it is attached on both sides to a radical. When this radical consists on both sides of methyl, we obtain the ketone known as acetone. This substance has received much attention on account of its having been found in the blood of diabetic patients, and it is suspected of causing diabetic coma; it produces intoxication and sleep, but it is less powerful than ether or chloroform. Lately a compound, in which the aldehyde group is attached on the one side to methyl and on the other to phenyl, has been introduced by Dujardin-Beaumetz. Its chemical name is phenyl-methyl-acetone or phenyl-methyl-ketone. It has received the name of

* Harnack and Witkowski, Arch. f. exp. Path. u. Pharm., xi., 21.

† *Vide* Appendix.

hypnone, but as it is quite clear that a very large number of ketones may have a hypnotic action, it is much better to give each its chemical name; for we may connect any radical—ethyl, butyl, propyl, etc.—to one or both sides of the CO group, and therefore the number of possible ketones is almost innumerable. When we consider that in addition to the ketones we have great possibilities amongst the alcohols and ethers, it is evident that a very large number of hypnotics may be obtained from the members of the alcohol series.

Action of Substituted Fatty Acids.

The hypnotic action of acids has already been referred to (pp. 99 and 113).

The replacement of an atom of hydrogen in the acids of the fatty series by chlorine, bromine, or iodine greatly increases their soporific action, either when they are given alone, or in the form of sodium salts. Thus sodium acetate has no more soporific action than common salt, but monochlor-acetate of sodium has a very marked narcotic effect. One would have been inclined to imagine that if the replacement of one atom of hydrogen by chlorine impart a soporific action to a substance, the replacement of two would increase this action, and of three would do so still more. But this is not the case, for while the sodium salt of monochlor-acetic acid has a markedly soporific action, that of dichlor-acetic acid is less so, and that of trichlor-acetic acid is so slight that a good deal of controversy has taken place as to its existence. This great difference in the action of these three bodies appears to be due to the comparative ease with which they undergo decomposition.* Monochlor-acetic acid is very unstable, trichlor-acetic acid is stable, and dichlor-acetic acid is intermediate between them. Monochlor-acetic acid or its sodium salt are decomposed when heated, or even when left at the temperature of the body, into sodium glycolate and hydrochloric acid, and the sodium salt is split up by carbonic acid into sodium carbonate

* Carl Frese, "Ueber die Wirkung der Monochloressigsaure und verwandter Körper." Inaug. Diss. Rostock, 1889.

and free monochlor-acetic acid. Dichlor-acetic acid decomposes in a somewhat similar way, but much more slowly, and yields also hydrochloric acid, but along with sodium glyoxalate. Trichlor-acetic acid decomposes in quite a different way and yields chloroform and carbonic acid. That the sopor caused by the sodium salts of the two first of these acids is due to the liberation of free acid in the cerebral cortex is rendered highly probable by the fact that when animals have been rendered drowsy by their administration it can be diminished by the injection of sodium carbonate into the vessels.

The replacement of hydrogen in acetic acid by bromine or iodine also imparts a narcotic action to the compound. But here also we are met by a curious and unexpected result, for the mono-iodo-acetic acid, instead of being very active, has comparatively little action, while mono-brom-acetic acid has got a most remarkable effect upon the muscles, rendering those of the frog so rigid that the animal may be held out by one leg, like a piece of wood. This action is also possessed to a less extent by mono-chlor-acetic acid. Other substituted fatty acids have a narcotic action, but, strangely enough, the replacement of hydrogen by chlorine sometimes lessens instead of increasing the narcotic properties. Thus crotonic acid is twice as powerful a narcotic as its substituted product, monochlor-crotonic acid, and sodium butyrate is more powerful a narcotic than sodium-trichlor-butyrate. It is therefore evident that the physiological action of a drug does not depend entirely on its chemical composition, nor yet on its chemical structure, so far as that can be indicated, even by a graphic formula, but upon conditions of solubility, instability, and molecular relations which we may hope to discover in the future, but with which we are as yet unacquainted.

Hypnotics related to Urea.

Urethanes—Chloralamide.

But there is another class of hypnotics, namely, those of which nitrogen may be said to form the basis, and which are closely allied to urea and uric acid. Urea, or carbamide, consists of two ami-

dogen groups, (NH_2), united to carboxyl, CO, thus $O{=}C{<}{NH_2 \atop NH_2}$. When one amidogen group is replaced by hydroxyl, OH, we get carbamic acid, thus: $O = C{<}{NH_2 \atop OH}$. This acid is not capable of independent existence, but its ammoniacal salt is familiar to us under the name of carbonate of ammonia (more properly ammonium carbamate). From its composition it seemed to Schmiedeberg likely that if carbamic acid were united to an alkyl, the alkyl would still continue to exert a narcotic action, while the NH_2, if it exerted any action, would tend to stimulate like ammonia. One would thus, he hoped, be able to get a hypnotic which would produce sleep, and in place of depressing the heart like chloral, would tend rather to stimulate it. Such a drug was likely to be useful in cases where, on account of cardiac feebleness, the administration of chloral might be dangerous. He accordingly tested the compounds of carbamic acid with methyl and ethyl. The latter substance is called urethane, from its relationship to urea on the one hand and ethyl on the other.

The term "urethanes" has also been given to all the members of the series in which alkyls are combined in a similar fashion with carbamic acid. The anticipations which Schmiedeberg formed have been realised, and urethane is a useful hypnotic, although not so powerful as chloral. One would imagine that urethanes containing alkyls higher in the series than ethyl would be more powerful, but unfortunately they are less soluble, and thus are rendered less active by their slow absorption.

In chloralamide the amidogen group (NH_2) is combined with chloral instead of with an alkyl, and it is calculated to combine the stimulating action of ammonia with the soporific action of chloral, and thus prevent any danger arising from the depressing effects of the chloral upon the heart. It consists of a combination of chloral with formamide, and appears to possess practically to a great extent the advantages which one would theoretically expect from it.

Chloral $CCl_3.COH$.
Formamide $COHNH_2$.
Chloralamide $CCl_3COHH.CONH_2$.

LOCAL ANÆSTHETICS.

In sleep, and to a still greater extent in the stupor produced by anæsthetic agents, impressions made upon the body may remain unfelt, although in the waking condition they might be painful. It frequently happens that we wish to prevent pain during a slight operation, or to relieve pain from some irritation without producing general stupor, and this we can sometimes do by means of local applications.

Cause of Pain.

The feeling of pain is undoubtedly due to some condition in the cerebrum itself, although it may be impossible for us to say where it is localised.

Tactile Centre.

The tactile centre has been located by Ferrier in the hippocampal region, and very probably the sensation of pain is also located here, for in some of his experiments I have seen a monkey in which this region has been destroyed give no evidence whatever of sensation, either tactile or painful, when the skin of the opposite part of the body was touched with a piece of wire sufficiently hot to make the animal jump when applied to the other side.

Peripheral Ends and Trunks.

As a rule the sensation of pain is awakened in the cerebral centre, wherever that may be, by stimuli applied to the peripheral ends of the afferent nerves. From these it is conveyed through the nerve trunks and spinal cord to the brain. There is a marked distinction between the sensibility of the peripheral ends and of the trunks of sensory nerves, the former being much more sensitive. On this account a stimulus applied to the skin may produce well-marked sensation, although a similar stimulus applied to the nerve trunks supplying that very piece of skin might not do so.

Nerve Trunks and Spinal Cord.

Pain may be occasioned by change in the nerve trunk or in the spinal cord, as well as by change in the peripheral ends,

and such pain is usually referred by the sensorium to the peripheral extremities, although these may be perfectly healthy as in cases of hysterical pains in joints, or may be absent altogether, as in the case of a man who complains of pain in the toes of a foot which has been amputated for years.

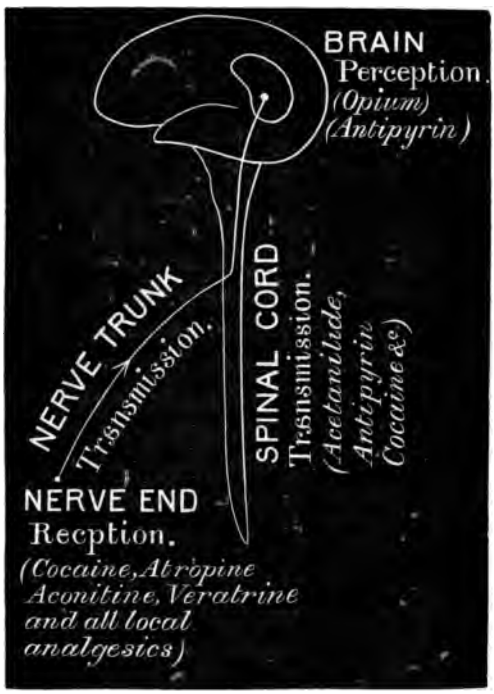


Fig. 23.

Diagram to illustrate the nervous mechanism by which painful impressions are received, conducted, and perceived, and the parts of this mechanism which are affected by particular analgesics.

Removal of Pain.

Pain due to irritation of any part of the sensory tract may be abolished by destroying the irritability of the part to which the irritant is applied, or the conducting power of the path by which it ought to travel to the brain.

Freezing.

One mode of producing local anæsthesia is by freezing. This can be done by ice and salt, but it is much more convenient and effective to use the cold generated during the evaporation of a volatile liquid, or, still better, of a gas which has been liquefied by cold and pressure. The spray of anhydrous ether was for a long time the most convenient form of producing local anæsthesia by the application of cold, but for two or three years back chloride of methyl compressed into iron cylinders has been found still more convenient. Whatever the means used, however, care is necessary to avoid destroying the tissues and causing ulceration, and this method is, therefore, by no means without its disadvantages.

Carbolic Acid.

Another method is to apply to the surface some drug which will destroy the sensation, and this power is possessed in a marked degree by carbolic acid. When applied to the skin it passes through the epidermis, gives rise to a certain feeling of burning, but produces at the same time such an amount of anæsthesia that boils may be opened without pain. Carbolic acid appears to have the peculiar power of irritating either peripheral ends or nerve centres, when applied to them, while if applied to nerve trunks it seems completely to destroy the power of conduction in the sensory fibres, without causing any irritation in them.

Cresols.

A local anæsthetic power is also possessed by several bodies allied to carbolic acid, such as para-cresol.* These substances destroy the sense of pain, but they do not destroy tactile sensibility. But carbolic acid coagulates albumen, and tends, like cold, to destroy the part to which it is applied, and to cause ulceration. A similar objection applies to a cresol. There are, however, other substances allied to carbolic acid, which are free from this objection. The most important of these is certainly cocaine (*vide* Appendix).

* Roger M'Neill, *Edin. Med. Journ.*, June, 1886, p. 115.

Cocaine.

When this substance is boiled with water it splits up, yielding methylic alcohol, benzoic acid, and another substance, ecgonine. From ecgonine, cocaine can again be built up by the addition to it of the radicals benzoyl, C_6H_5CO, and methyl, CH_3. Ecgonine has no local anæsthetic action whatever, and in this it resembles tropine, which is a product of the decomposition of atropine (*vide* Appendix).

Atropine.

Atropine splits up into tropic acid and tropine, which has no local anæsthetic action, although atropine possesses it to a certain extent; but when tropine is combined with benzoic acid instead of tropic acid, the resulting benzoyl-tropine, or homatropine, has a distinct local anæsthetic action.

Benzoyl Compounds.

This fact led Filehne to suspect that the anæsthetic property in cocaine probably resided in the benzoyl rather than in the ecgonine. Curiously enough, benzoyl-ecgonine does not appear to have a distinct local anæsthetic action, although the addition of methyl, which converts it into cocaine, gives it this power in such an eminent degree.* Yet Filehne's supposition is, to a great extent, correct, and he has found that the benzoyl derivatives of several substances have a marked local anæsthetic action. Amongst these are the benzoyl derivatives of morphine, hydrocotarnine, quinine, cinchonine, and methyl triacetonalkanine. The latter has, next to benzoyl-tropine, most resemblance in its action to cocaine. Next comes benzoyl-quinine, and the weakest is benzoyl-morphine. Unfortunately, these substances, with the exception of benzoyl-tropine, have all an irritant action, which precedes their anæsthetic action, and when introduced into the

* A similar effect is produced by ethyl, which converts benzoyl-ecgonine into cocethyline, a body having anæsthetic properties like cocaine, but without its power to dilate the pupil, and much less poisonous. Merck, *Ueber Cocaine Diss.* Kiel, 1886.

eye they cause so much burning that they cannot be used as local anæsthetics. Benzoyl-tropine, although free from this objection, acts too much like atropine, and therefore is for many purposes inadmissible.

Anæsthetica Dolorosa.

The irritant action which a number of local anæsthetics possess has led Liebreich to divide local anæsthetics into two classes: those which cause local irritation and pain, and those which do not. In a letter to the *Lancet* * I suggested that most of the substances belonging to the group of cardiac poisons, like digitalis, might have a local anæsthetic action. At that time I was unaware that they had nearly all been tested and found to have such an action by Professor Hoppe.† Unfortunately, however, they nearly all cause more or less irritation before producing their anæsthetic action, and are practically not available.

* *Lancet*, March 3rd, 1888, p. 446.

† I. Hoppe, "Die Nervenwirkungen der Heilmittel," 1856 (Leipzig, Hermann Bethmann).

LECTURE IV.

CONTROL AND CURE OF DISEASE (*Continued*).

ANALGESICS.

Non-reception and Non-perception of Painful Stimuli.

The two classes of drugs which we have already considered, general anæsthetics and local anæsthetics, both abolish pain: the latter by acting upon the peripheral terminations of sensory nerves, so that they do not receive the painful stimuli; and the former upon the nerve centres, so that they do not perceive them.

Non-transmission of Painful Stimuli.

But pain will also be relieved if the conducting power of the sensory nerve trunks or of the sensory paths in the spinal cord be so altered that painful impressions can be no longer transmitted.

Action of Cocaine on Nerve Trunks.

Cocaine has this effect upon nerve trunks when locally applied, for, when injected subcutaneously near a nerve, it may produce anæsthesia in all the district to which that nerve is distributed.*

Action of Cocaine on the Spinal Cord.

It has a similar action on the sensory tracts of the spinal cord, or Hughes Bennett † found that it rendered these tracts insusceptible to stimulation; and Mosso ‡ found that both conductivity and reflex excitability in the cord are destroyed by it before the nerve trunks, either sensory or motor, are paralysed.

Action of Cocaine on the Cerebral Cortex.

It lessens the irritability of the cerebral cortex when directly

* Hall and Halstead, *New York Medical Journ.*, Dec. 6th, 1884.
† Hughes Bennett, *Edin. Med. Journ.*, Oct., 1873.
‡ Ugolino Mosso, *Arch. f. exp. Path. u. Pharm.*, vol. xxiii., p. 153.

applied, for if a 4 per cent. solution be applied to the motor areas, no convulsions can be produced by irritation by a faradic current.*

Excitability and Conductivity.

We must distinguish between excitability and conductivity both in nerve trunks and in the spinal cord. For these two functions of nerve fibres are to a certain extent independent of each other, and a nerve fibre may still be able to conduct stimuli from the peripheral terminations to the nerve centres, and *vice versâ*, when irritation applied to the nerve trunk produces no apparent effect. This condition may occur after exposure to great cold, and also in some pathological conditions.

Action of Drugs on the Conducting Power of Nerve Fibres.

Loss of conductivity may also be produced by the application of various substances to the nerve trunks, and a knowledge of the effect of drugs on the conducting power of nerve fibres appears to me absolutely necessary in order to understand the action of drugs on the spinal cord or on the higher nerve centres. For in the cord and brain the nerves cells and nerve fibres are so closely associated that it is very difficult, if not impossible, to separate the action of a drug on the one from its action on the other. But in the nerve trunks we can apply the drug to nerve fibres alone. Having thus ascertained its action upon them, we may be able to judge with greater certainty what part of the drug's effect on the spinal cord is due to its action on the fibres, and what to its action on the cells.

For this reason I thought it necessary to begin a research on this subject along with my assistants, Dr. Batten and Mr. Bokenham.

The method employed was to take the sciatic nerve of a frog, with the gastrocnemius muscle attached, so that its contraction or non-contraction when the nerve was stimulated might serve as an index for the presence or absence of functional activity in the nerve.

The nerve could be stimulated by a faradic current, either at

* Tumass, *Arch. f. exp. Path. u. Pharm.*, vol. xxii., p. 107.

the end A, farthest from the muscle M, or at a point B nearer the muscle. A large portion of the nerve was placed in a small glass chamber C, into which various vapours or liquids could be introduced at will, so as to act on the nerve trunk. When the nerve was in its normal condition, the muscle M contracted on stimulation of the nerve either at A or B. But if carbonic acid was introduced into the chamber it abolished the irritability of that part of the nerve on which it acted, so that stimulation at B no longer caused any contraction of the muscle. But it did not destroy the conductivity nearly so quickly, for a stimulus applied at A would be conducted to the muscle, and cause contraction, when one applied at B had ceased to have any effect. Alcohol and ether had just the opposite effect, for they destroyed conductivity before irritability, so that stimulation at A had no effect, while it caused contraction if applied at B. Phenol acted

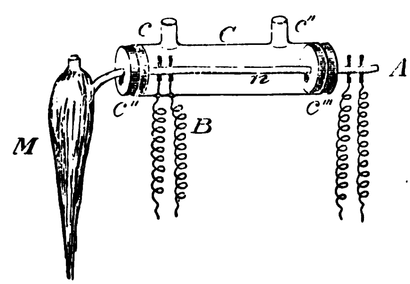


Fig. 24.

Diagram to illustrate the action of drugs on the excitability and conductivity of nerve trunks. C, a chamber with two openings, *c* and *c''*, through which vapours or gas can be introduced and closed at both ends by soft material, through which the nerve *n* can pass without being injured or compressed. M is a frog's muscle. A and B are two sets of electrodes by which the nerve can be stimulated.

like carbonic acid, and destroyed irritability before conductivity. The action of dimethyl-benzene differed according to the position of the methyl groups. Ortho-dimethyl-benzene or ortho-xylene had almost no action; para-xylene increased the irritability of the nerve, so that a single stimulation caused

tetanus, and meta-xylene did the same to a still greater extent. The number of substances experimented with has been considerable, but it would occupy too much time to discuss the results now. I would merely draw attention to the action of xylenes as having a possible bearing on the action of analgesics.

Mode of Action of Analgesics.

But our knowledge of the conduction of impressions in nerve trunks and the spinal cord is insufficient as yet to explain either the physiology of pain or the action of analgesics. We frequently notice that a very small dose of laudanum, such as 3 or 5 minims, will relieve abdominal pain without producing the least drowsiness, or, indeed, without exerting any other apparent effect upon the organism; and a similar result may be observed in severe headache from the administration of 5 or 10 grains of antipyrin. In trying to explain such phenomena we are obliged to have recourse to hypotheses.

Use of Hypotheses.

A hypothesis in itself has no value, and is worse than useless if it leads people away from facts, but it is extremely useful when limited to its proper function, namely, to help us to string together facts which are already known, and to indicate the direction in which to look for new ones. Thus Dalton's atomic theory has been of the utmost value to chemistry, and the hypothesis that the carbon atoms are united into a ring has not only rendered the classification of aromatic compounds much easier, but it has aided in the discovery of new ones.

Facts regarding the Transmission of Painful Impressions.

As the first function of the hypothesis is to link facts together, let us first see what facts we have got in relation to pain. Painful impressions are conveyed by the grey substance in the spinal cord. This seems to be shown both by physiological experiments and by clinical observations. Tactile impressions are conveyed by the white matter, probably in the lateral columns. Tactile

impressions are conducted more quickly to the brain than painful ones, and a more powerful stimulus is required to produce a painful impression than a tactile one.

Fibres and Cells as Conductors.

This is exactly what one would expect from the different nature of the conducting paths of the two instances; for the nerve fibres which conduct the tactile impression have an almost direct course, and afford little opportunity for any weakening of the stimulus by diffusion. The branching cells of the grey substance, on the contrary, form a zigzag path which must be longer than the other; it probably presents greater resistance and it affords more opportunity for entire loss of the stimulus by diffusion to other cells in the cord. Thus, unless the stimulus is tolerably powerful, none of it may pass upwards to the brain, and therefore no painful sensation will be perceived.

Summation in Cells.

But, on the other hand, it would appear that the cells of the grey substance in the spinal cord or the sensory ganglia of the brain may be so excited by a succession of very feeble stimuli, each reinforcing the other, that the extremest agony may be produced. Thus we have all heard that one of the most dreadful tortures of the Spanish Inquisition consisted in allowing a single drop of water to fall at regular intervals; and Naunyn* has found that in some cases of spinal disease intense pain may be caused by gently touching the foot with a point of a camel's-hair pencil at regular intervals. A summation of the stimuli appears to go on in the cells, each stimulus increasing the effect of the preceding, just as a slight touch upon a swing, repeated at the proper moment, will send it higher and higher and higher until it oscillates to the fullest extent of which it is capable.

Effect of Stimuli depends on Time of Application.

But if similar touches be applied to the swing so as to interfere

* Naunyn, *Arch. f. exp. Path u. Pharm.*, vol xxv., p. 301.

with, instead of to assist its oscillation, they will soon bring it to rest. Similar touches will thus produce opposite effects from a change in their relations to the oscillation of the swing. Translating this into physiological language, we should say that in the first instance we had a case of summation, in the latter of inhibition. Let us follow this familiar illustration one step farther. We all know that when we start a swing we stand close to it at the spot where it hangs when it rests, and as its oscillations get longer and longer we move farther back. If we move a little way back our pushes will first have the effect of summation, but if we remain in that position and do not adapt our pushes to the increasing oscillation of the swing, they will lessen instead of increasing its movements, or, in other words, they will have an inhibitory action. Thus we will have stimuli producing alternately an increase and a diminution in the oscillations in the swing, though the increase and diminution will not be very great.

Alternate Stimulation and Inhibition in Health.

We seem to have a somewhat similar condition in the nervous system. Some time ago I was making some experiments with one of Mr. Francis Galton's whistles, which he kindly lent me. I adjusted it so that the sound produced was almost at the upper limit of my sense of hearing. On then sounding it continuously I was struck by the fact that the sound was alternately audible and inaudible, although I ascertained that no corresponding change occurred in the strength with which the whistle was blown.

In Disease.

A similar observation was made by the younger Remak* in relation to pain in a case of tabes dorsalis. He found that when a faradic current was applied by a brush the sensation it produced gradually increased, then diminished, and increased again, although the strength of the current remained perfectly the same. With a weak current the increase each time became less, and the pauses between became greater, until at last no sensation was

* Remak, *Arch. f. Psych. u. Nervenkrank*, vol. vii., p. 505.

felt. With a stronger current the sensation gradually increased until it became so painful as to be unendurable.

Possible Effect of the Blood.

In my own case I was unable to satisfy myself that the alternate appearance and disappearance of the sound of Galton's whistle might not be due to an alternate increase in the sensibility of my auditory centres from altered supply of blood, for I observed * some years ago a capillary pulsation in man which usually occurs about once in twenty seconds, and this appeared to be nearly the time of each wave of hearing. In Remak's case the waves of sensation were from twenty to fifty seconds, and the alteration in the length of interval between them renders it probable that they were due to summation in the nervous system itself rather than to alteration in its vascular supply.

ANALOGY BETWEEN SENSATION AND MOTION.

Summation of Motor Stimuli.

A marked analogy seems to exist between sensory and motor processes in the spinal cord. In a research which Stirling made under Ludwig's direction, he showed that reflex contractions only occur from repeated shocks to the nerve centres—that is, through summation of successive stimuli.†

Summation of Sensory Stimuli.

According to Naunyn the same rule holds good for pain, which he regards as also a consequence of summation. For this reason it can only occur when conduction through the grey substance is not so much disturbed, because it is only in the grey substance that summation can take place, the structures of the white columns not being adapted for it.

* Lauder Brunton, *Journal of Physiology*, vol. v., p. 14.

† Stirling, Ludwig's Arbeiten, 9ter Jahrg., p. 290; Sitz. Ber. d. k. Sach. Gesell. d. Wiss., Bd. xxvi. p. 439.

Summation in Peripheral Nerves.

But if the analogy between sensory and motor processes be true in the spinal cord, we should expect to find something similar in the peripheral ends of nerves.

Tickled to Death.

There is no phenomenon in physiology which strikes me as more wonderful than the extraordinary motor effects which can be produced by the application of extremely slight stimuli to the skin, phenomena which seem utterly disproportioned in their extent to the slightness of their cause. I well remember, as one of the most frightful moments of my life, being nearly tickled to death by a nurse. I do not think I could have been more than five years of age, but the agony of that moment is deeply imprinted in my memory, and I can well believe the truth of the statement that Simon de Montfort, during the persecution of the Albigenses, put some of them to death by tickling the soles of their feet with a feather. Yet of all parts of the body the skin of the soles of the feet is liable to the most constant and severe stimulation in walking, running, and leaping. It has sometimes occurred to me that possibly the different effect of a slight stimulus like the touch of a feather, which causes intense reflex action, and of a gentle but steady pressure of the finger, which gives rise to no reflex action at all, may be due to the stimulation by the latter of two sets of nerves which counteract or inhibit each other.* The prolonged course of the nerve fibres in some of the tactile corpuscles may possibly have something to do with this. A similar phenomenon to the effect of steady pressure in lessening reflex action may be observed in the relief afforded by rubbing or stroking a part which has been pinched or bruised, or by scratching an itching spot.

Transference of Hysterical Hemi-Anæsthesia.

But this is much less in degree and is by no means striking,

* Lauder Brunton on Inhibition, West Riding Asylum Reports, 1874, p. 179, and "Nature," 1883, vol. xxvii.

while the transference of hemi-anæsthesia to the other side of the body in hysterical patients by the simple application of a piece of metal or even a wooden button is comparable to death from tickling, both in the extraordinary character of the result and the slightness of the cause.

Mode of Action of Analgesics.

In considering the action of analgesics we must take into account their possible effect on nerve endings, peripheral and central, as well as their action upon nerve trunks and nerve cells. It is *à priori* probable that when the blood contains any drug having the power to lower the activity of nerve fibres its action will be exerted upon the peripheral ends before they have received a medullary sheath, and at the central ends where they have lost it, at their junction with nerve cells, before it can act on the nerve trunks. For not only is a nerve trunk sparingly supplied with blood, but the medullary sheath will oppose a certain obstacle to the action of drugs upon the axis cylinder. This appears to be the case with cocaine; for at a certain stage of poisoning irritation of the nerve trunks will produce reflex action, although irritation of the skin is no longer followed by any response, a fact which indicates that the peripheral terminations of the nerves have been paralysed before the fibres in the trunk.

Explanations.

Dealing with hypotheses, as we must do in relation to the action of analgesics, one of the first explanations that occurs to us as probable is that the sensory impulses which in the normal condition would give rise to summation in the cord or sensory ganglia, and, being transmitted to the brain, give rise to pain, may be diffused from one cell to another, and the impulses, instead of causing summation, may even produce inhibition.

Possible Failure of Analgesics to Relieve Pain.

It is evident that if the relief of pain by analgesics is due to the diffusion of a sensory stimulus, so that it does not reach the brain,

it is quite possible for a very powerful stimulus to pass to the sensory centre in spite of a loss by diffusion. In such a case the pain might actually undergo a process of summation in the cord and be rendered more excruciating instead of being relieved by the remedy.

Irradiation of Motor Impulses Produced by Analgesics.

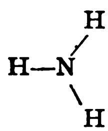
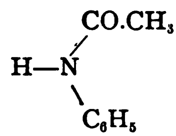
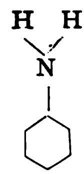
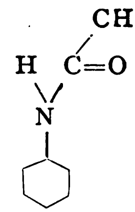
There appears to be, as I have said, a resemblance between the sensory and motor processes in the cord, and most of the analgesics, as distinguished from the anæsthetics, tend to cause irradiation of motor impulses. While anæsthetics lessen the activity of all the nervous tissues and thus produce drowsiness, loss of sensation, and abolition of motor power and reflex action, many of the analgesics, when pushed to excess, tend to produce excitement of the reflex action with diffusion of movement. Thus, when the toes of a frog are slightly pressed it only draws the foot away, but in a frog poisoned by an overdose of some of the analgesics the stimulus, instead of being localised in the cord and producing a reflex action limited to one limb, appears to be diffused through the nervous system generally, giving rise to tremor over the whole body, or even to convulsions and tetanus. This condition is observed when frogs are poisoned by the most powerful of all analgesics, namely, morphine, and it is common to most of the others—cocaine, antipyrin, antifebrin, phenacetine, and exalgine.

CHEMICAL STRUCTURE OF ANALGESICS.

All those substances belong to the aromatic group of bodies, and it is in this group that we are likely to find the most powerful drugs to relieve pain as well as to reduce temperature. The constitution of morphine * is very complicated, and we do not yet know what it is; all that can be said about it is, that it is probably a quinoline of phenanthrene. Antifebrin, or, as it is scientifically

* Morphine is a most powerful antipyretic in birds, reducing the temperature of pigeons sometimes as much as 7°. Brunton and Cash. *Centralblatt f. d. Med. Wiss.*, No. 14, 1886; and Beitr. z Physiol., Carl Ludwig zu seinem 70sten Geburtstag gewidmet., 1887. Leipzig: Vogel.

called, acetanilid, or phenylacetamide, has the simplest constitution of any of the bodies that I have mentioned, for it merely consists of aniline in which one atom of hydrogen is replaced by

Ammonia. Phenylacetamide. Aniline. Acetanilid.

acetyl. You will see from its formula that it may be regarded as ammonia, in which one atom of hydrogen is replaced by phenyl, and another by acetyl. When regarded from this point of view it is called phenylacetamide. But it may be regarded also as benzene in which one atom of hydrogen has been replaced by NH_2, and thus converted into aniline, and then an atom of H in the NH_2 has been replaced by acetyl $CO.CH_3$. When regarded from this point of view it is called acetanilid. In two long researches on which Dr. Cash and I have been engaged for more than six years, as well as in some experiments in aid of which I obtained a grant from the Royal Society, fifteen years ago, we have been trying to ascertain the effect of ammonia and its various compounds on the one hand, and of substances belonging to the aromatic or benzene series on the other, upon muscle, nerve, and nerve centres.*

Action of Ammoniacal Compounds.

In the course of the research we found that ammonia and its salts stimulate and afterwards paralyse the spinal cord. The stimulant action was marked in ammonia, ammonium bromide, and ammonium chloride. The paralysing action was more marked in the case of the iodide. The compound ammonias have a much more powerful paralysing action both on the spinal cord and on the motor nerves, especially on the latter, and here again the paralysing action is most marked in the case of the iodides.

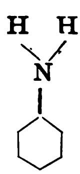
* Brunton and Cash, Phil. Trans., Part I., 1884.

Action of Aromatic Compounds.

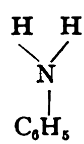
The aromatic compounds all tend to produce increased sensibility, inco-ordination, and tremor, but they do not all seem to affect the spinal cord alike, for while benzene and its haloid compounds, mono-chlor-, mono-brom-, and mono-iodo-benzene, produce in frogs tremors, which remind one of disseminated sclerosis in man, with ethyl benzene the movements of the frog's legs were short, flapping, and ineffective, reminding one of locomotor ataxy in man.

Effect of Combination with Amidogen upon Aromatic Bodies.
Action of Amido-compounds—Aniline.

Aniline may be regarded either as amido-benzene, that is, benzene, C_6H_6, in which one atom of hydrogen is replaced by amidogen, NH_2, or as phenylamine, that is, ammonia, in which one atom of hydrogen has been replaced by phenyl, C_6H_5.



Aniline as represented as Amido-benzene



Aniline represented as Phenylamine.

In accordance with this constitution we found that the symptoms produced by it were different both from those of benzene and those of ammonia. They differ from those of benzene, and resemble those of ammonia in the tendency to more violent spasm and to greater paralysis of muscle and nerve.

They differ from those of ammonia, inasmuch as the convulsion never assumes the form of true tetanus, the tetanic spasm which the ammonia group would produce being broken up, so to speak, by the action of the benzene.

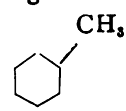
Tetanising Agents ought to be Analgesics.

If the hypothesis be correct that a relationship exists between the power of a drug to cause diffusion of sensory and of motor stimuli

in the cord, one would expect that substances which cause tetanus, like ammonia, chloride of ammonium, and strychnine, ought to act in some measure as analgesics. Indeed, this seems to be the case, for ammonium chloride is sometimes a very successful remedy in the treament of neuralgia, and strychnine is sometimes useful in the lightning pains of locomotor ataxy. But the fact that ammonia, benzene, and ethyl benzene, while all tending to produce spasm, cause movements of such different kinds, indicates that they affect the motor parts of the spinal cord in different ways. We might, therefore, expect that similar differences would exist in the sensory parts of the cord, and thus one drug might have a special tendency not only to relieve pain in general, but to relieve a particular sort of pain more than another.

According to Dujardin-Beaumetz,* the power to relieve pain is most marked in those amidogen derivatives of the aromatic group in which an atom of hydrogen is replaced by an alkyl and especially by methyl, while the amidogen derivatives, where no such substitution has taken place, have their antipyretic action most marked. Thus acetanilide, which is an amidogen derivative of benzene, is a powerful antipyretic. It has also an analgesic action,† but when it is combined with methyl its analgesic power is increased.

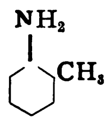
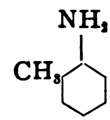
Constitution of Acetanilides in Relation to their Action.

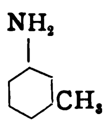
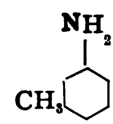
When the methyl group CH_3 is connected directly with the benzene nucleus, replacing an atom of hydrogen in benzene, the body $C_6H_5CH_3$ or  is called toluene, and as the nucleus is symmetrical the resulting body is identical, whatever carbon atom in the benzene ring the methyl may be attached to. But this is not the case if one atom of hydrogen in the ring has already been replaced by amidogen, and it then becomes a matter of considerable importance where the methyl group CH_3 is placed. There are three positions in

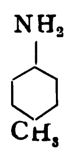
* Dujardin-Beaumetz and Bardet, *Compt. Rend.*, cviii., p. 571.

† Lépine, *Rev. de Méd.*, 1887, pp. 306, 520.

relation to the amidogen group (NH_2) where it can be placed in the benzene nucleus, and these are called the ortho-, meta-, and para- positions, thus :—

the ortho  or 

the meta  or 

and the para 

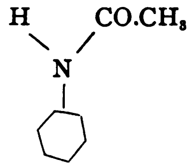
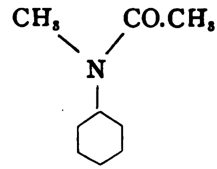
The bodies in which both the amidogen NH_2 and the methyl CH_3 groups are connected directly with the benzene ring are called *toluides*, and the three just mentioned are called ortho-, meta-, and para-toluide respectively.

When one atom of hydrogen in the amidogen group is replaced by acetyl $CO.CH_3$ in one of those bodies, in the same way as in acetanilide, they become acet-toluides.

According to Jaffe and Hilbert, the meta-aceto-toluide is the only one which retains the antipyretic action, the compound in which the methyl is in the para position being inactive and the ortho-compound being toxic, causing acute nephritis, but not antipyretic.

Exalgine.

But instead of being directly connected with the benzene nucleus the methyl group CH_3 may replace the remaining atom of hydrogen in the amidogen group of acetanilide, and thus methyl acetanilide is formed.

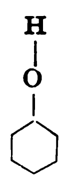
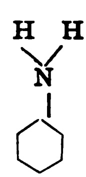
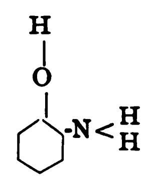



Acetanilide. Methyl Acetanilide or Exalgin.

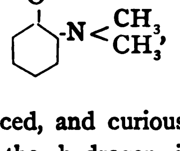
This compound has been investigated by Dujardin Beaumetz and Bardet, and they have found that it has a marked analgesic power, so great that they think it deserves the name of exalgine. According to them its power to relieve pain is very marked in all kinds of neuralgia, and is greater than that of antipyrin.

Effect of Alkyls on Aromatic Compounds.

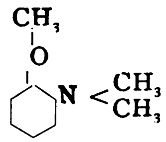
Another most interesting research on the effect of introducing alkyls into aromatic compounds has been made by Baldi under Schmiedeberg's direction. Curiously enough, though phenol and aniline are both poisonous, yet ortho-amido-phenol is not poisonous. If the two hydrogen atoms in the

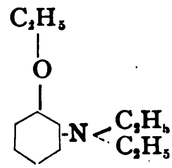
Phenol. Aniline. Ortho-amido-phenol.

amidogen group in this body are replaced by two methyls, thus—  an extremely weak narcotic substance is produced, and curiously enough the narcotic action is still weaker if the hydrogen in the hydroxyl is also re-

placed by methyl,



. But if all three hydrogens are replaced by ethyl,



, the substance has a distinct narcotic action, and the body,

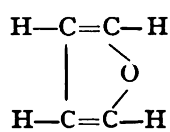
$$C_6H_4\begin{cases} O.\,CO.\,OC_2\,H_5 \\ NH_2 \end{cases}$$

has a powerful analgesic action.

Analgesics from the Intermediate or Furfuryl series—Antipyrin.

I have already mentioned, pp. 27 and 49, that between the fatty, or alcoholic, and the aromatic series, there is another which is intermediate both in the mode of linkage of the carbon atoms and the stability of their connection.

As an example of this series we have furfuran—

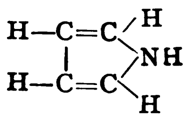


When the oxygen in furfuran is replaced by the imidogen group NH we have *pyrrol.* When one C in pyrrol is replaced by N we get *pyrazol.*

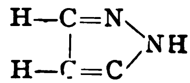
By the action of reducing agents this takes up two atoms of hydrogen, becoming pyrazolin, and from this results pyrazolon by the replacement of CH_2 by CO.

From pyrazolon is derived dimethyl-phenyl-pyrazolon, better known as antipyrin, which as it contains phenyl C_6H_5, belongs to the aromatic as well as the intermediate series.

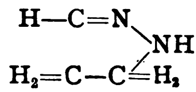
The relationships of these substances may be seen from the following graphic formula:



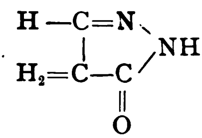
Pyrrol.



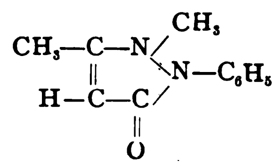
Pyrazol.



Pyrazolin.



Pyrazolon.



Antipyrin.

Prospect of Numerous Analgesics.

As the ways in which methyl may be combined with aromatic bodies are almost numberless, we may expect before long a great increase in the number of analgesics, and not improbably some new ones may far surpass in their power to relieve pain anything that we as yet possess. Before passing from this subject, however, I must indicate a possible source of danger from the continued employment of such analgesics.

Dangers from Analgesics.

We know that the continuous employment of narcotics, such as morphine or chloral, is apt to grow into a habit, and the con sequences may be very deleterious to the mental functions. A similar habit, we know, may be established by the use of cocaine and it is possible that something similar may occur in the case of other analgesics. But there is another possibility which I wish to indicate in addition to this, namely, that just as the brain may become deteriorated by the use of chloral or morphine, so the cord may possibly be injured by the use of analgesics. I have already mentioned that Dr. Cash and I observed in frogs symptoms resembling those of disseminated sclerosis, or of locomotor ataxy in man, and my assistants, Drs. Batten and Bokenham, have noticed that antipyrin may produce in frogs a condition like that of

spastic paralysis. Cash and I tried to produce symptoms of permanent disease of the spinal cord in frogs by keeping up the poisoning for some time. We were unsuccessful in the attempt, as the symptoms always passed off when the poison was eliminated, but still the conditions in our experiment were very different from those which would occur from the prolonged use of analgesics by a patient, inasmuch as the treatment of the latter might continue for weeks, months, or years, whereas in our experiment time could be counted by days. A circumstance that renders circumspection in the use of analgesics all the more necessary is that various nervous disorders in which the symptoms appear to depend either upon peripheral neuritis or an affection of the spinal cord have lately been described as arising from the use of some of the new explosives, whose chemical constitution approximates somewhat to that of the analgesics.

Another action of analgesics which renders caution desirable in their use is their effect upon the blood. Thus exalgine may render the blood incapable of performing its respiratory functions, and thus induce marked lividity, with tendency to collapse, and in this way endanger life, while others may destroy the blood corpuscles and produce marked anæmia.

Possible Relation of Leucomaines or Ptomaines to Spinal Disease.

In relation to this, another question suggests itself: whether diseases of the spinal cord may not owe their origin, at least in part, to poisons of the aromatic series, generated either in the intestinal canal or in the tissues of the cord itself.*

Use of Suspension.

The remarkable benefit obtained from suspension in cases of locomotor ataxy is one of the most striking discoveries that have been made in therapeutics of recent years. It is very difficult to explain, but I should be inclined to think that suspension merely acted upon the cord in the same way that massage does upon the

* It is to be remarked that pyrocatechin, a body belonging to this series and having a very powerful action on the spinal cord, is so commonly found in human urine as to be almost a normal constituent.

muscles, by removing the lymph, and with it the products of nerve waste; while, at the same time, it may increase the processes of oxidation and repair by promoting a free circulation of the blood.

ACTION OF DRUGS ON THE CIRCULATION.

The state of a patient's circulation has always been regarded as the most important guide the physician can have in regard both to prognosis and treatment. The arms of our College exhibit a hand feeling the pulse as the most characteristic act of a physician.

Fig. 25.
Arms of the Royal College of Physicians.

Test for Life.

As the old adage has it, "While there is life there is hope," and life can never be regarded as extinct while circulation continues. One of the best, if not the best, tests whether life is actually extinct or not is to tie a piece of thread with moderate tightness round the finger. If the person be quite dead no change will occur, but if there be any circulation, however slight, the end of the finger will gradually swell. Even after death has occurred and circulation has ceased in the body generally, we are able to maintain the functional activity of isolated organs by means of artificial circulation, so that the lung retains its vitality, the muscles their conductivity, and the glands their secreting power for hours or even for days after the rest of the body to which they belonged are dead. On the other hand, if the circulation in an organ be arrested by contraction, plugging, or pressure upon

the vessels supplying it, its function is quickly abolished, although the other parts of the body may be perfectly healthy.

"Faint Heart never Won Fair Lady."

Feeble circulation leads to poor nutrition and general weakness and inefficiency, so that a faint heart has become proverbially unsuccessful. A stout or strong heart, on the other hand, leads to active circulation, good nutrition, general power, and success in life. By keeping up an abundant supply of blood to the tissues, it removes the acid products of waste which, as we have seen, powerfully tend to interfere with oxidation. But possibly this is not the only effect of a powerful heart.

Chemical Uses of the Pulse.

According to Fleischl, the shock of the blood sent into the capillaries at each cardiac systole has a mechanical action in aiding the chemical processes of tissue change, in somewhat the same way, though to a less extent, as a blow upon a percussion cap. If the heart is too feeble, or the resistance in the vessels too great, to allow the blood entering the aorta at each systole to give a distinct forcible impulse to the blood present in the arteries the chemical changes in the tissues will be sluggish and imperfect. It is therefore of the utmost importance in the treatment of disease to maintain the action of the heart, and to stimulate it when it is flagging.

Beef-tea as a Cardiac Stimulant.

It is curious to note how a well-grounded practice often holds its own amid changes of theory, and beef-tea still maintains a foremost position amongst our cardiac stimulants. We have other drugs which increase the power of the heart, and which are most useful in their place: digitalis, strophanthus, convallaria, adonis vernalis, and erythrophlœum, and the whole class of drugs usually known as cardiac poisons. Unfortunately these drugs do not always give us the result we desire, and at present we are often un-

able to say why they fail. We do not know their chemical constitution, and therefore we cannot modify or produce at will drugs having a similar but not identical action, as we can, to a certain extent, in the case of antipyretics and analgesics. Starting from beef-tea, however, we may perhaps obtain what we want. One of the constituents of beef-tea is xanthine. This has a very powerful action on voluntary muscular fibre, but its effect on the heart requires to be more carefully made out.

Caffeine as a Cardiac Tonic.

Tri-methyl-xanthine, or caffeine, is now recognised as an important cardiac tonic. Like xanthine, it tends to increase the contraction of muscular fibre, both voluntary and involuntary, and, when its action is pushed far enough, it produces an extraordinary state of muscular rigor. In consequence of this, voluntary muscles dipped into a solution of it frequently contract to the utmost extent of which they are capable, and when applied to the frog's heart it causes the beats to become slower and the heart more and more contracted, until it ceases to beat in systole. In this action it agrees with the other cardiac tonics, like digitalis; but a curious point is here to be noted.

Paradoxical Action of Caffeine.

Although it usually causes firm contraction of the frog's muscles yet sometimes it causes none at all, and Cash and I have actually found it cause elongation. At present we are unable to explain this curious phenomenon with certainty.

Possible Transverse Contraction and Active Elongation of Muscle.

To me it seems most readily explained on the supposition that muscular fibre, both voluntary and involuntary, not only contracts longitudinally and thus becomes shorter, but may contract transversely and thus become longer. The varying conditions, which Cash and I have observed in the frog's muscle under the influence

of caffeine,* may be explained by supposing that usu
tudinal contraction is greater than the transverse,

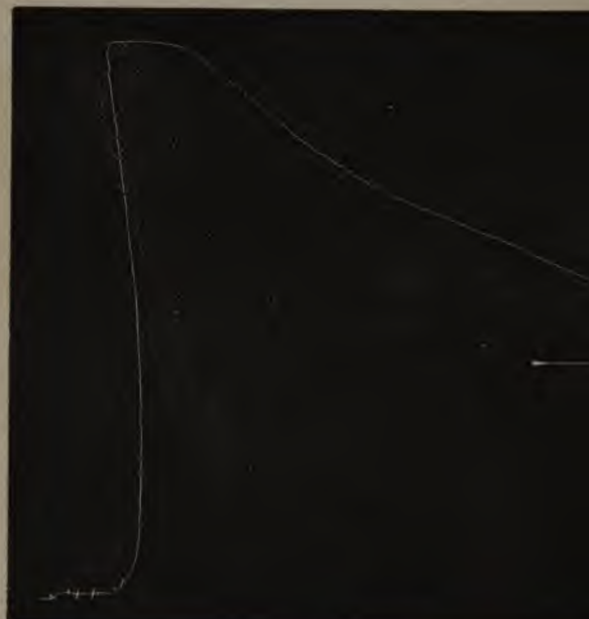


Fig. 26.
Action of caffeine on the gastrocnemius of the frog.
spended, 10 grammes in all. Lever multiplies 1

the muscle shortens; that occasionally the longitudir
verse contraction occur together and counteract ea
that the muscle retains its usual length; and final
sionally, though rarely, the transverse is greater th
tudinal contraction, and therefore the muscle becom

Practical Bearing of Physiological Question

But some men may say, What does it matter to

* Caffeine and theine are usually regarded as identical, alt
probable, from differences observed by Mays in their action on
and by Cash and myself on muscle, that they may not be so.

which will give us most assistance in treatment, after we have once learned the causes of these differences. Caffeine usually, as I have said, contracts the muscles of the frog's legs, but sometimes it elongates them, and the same difference in its action is observed in the heart. Generally the heart stops in systole, but sometimes it stops in full diastole. In this respect the action of caffeine resembles that of digitalis.*

Complexity of the Heart.

In the heart we are not dealing with muscular fibre only, but with nerves and ganglia as well, and the effect of any drug upon this organ is the resultant of its action, not only upon all these structures in the heart, but also upon the medulla. Moreover, when we are dealing with the heart in connection with the blood-vessels the action becomes still more complex, for contraction or relaxation of the vessels will alter the resistance which the heart has to overcome. The problems we have to solve in looking for new cardiac tonics are, therefore, far from easy, but we may hope that patient investigation will solve them, and that we may ere long aid the sufferers from cardiac disease more efficiently than we can at present.

Direction in which to Look for Cardiac Tonics.

I have already pointed out that most drugs belonging to the class of cardiac tonics are also local anæsthetics, but all local anæsthetics do not appear to be cardiac tonics. Nevertheless, by looking through the class of local anæsthetics we may perhaps find some new cardiac tonics, and at any rate, it is worth while to try.

ACTION OF DRUGS ON THE BLOOD-VESSELS.

Our knowledge of the chemical nature of drugs which dilate the blood-vessels is somewhat greater than of those that contract them, for the agents which cause dilatation most markedly are of very simple chemical structure. They are, in fact, nitrites, or

* Cf. Lauder Brunton "On Digitalis," pp. 96 and 108. London: Churchill. 1868.

Necessity of Investigation of the Action of Simple Drugs on Simple Tissues.

It is only by a thorough knowledge of the conditions which cause bodies of simple chemical structure like caffeine or xanthine sometimes to produce contraction and sometimes elongation of muscle that we can hope to treat cardiac disease with certainty, either by means of these substances or by more complex cardiac tonics. The only indication that we have of life is motion, either of the body as a whole or its parts, as in the movements of the respiration or pulse, or of the blood in the test for life I have already mentioned, or in secretion, as in the case of glands kept alive by artificial circulation. In order to understand thoroughly the effect of any drug we must know what its action is upon muscular fibres, and the variations produced in its action by changes in the temperature or reaction. But muscular fibres are usually stimulated to contraction or to relaxation by efferent nerves, and they are again excited by the nerve centres from which they proceed. Unless we know the action of drugs on nerves as well as on muscles, we cannot rightly estimate their action upon nerve centres. It is on this account that Cash and I have not only taken up the study of comparatively simple drugs, such as ammonia, compound ammonias, alkalis, earths, and the simpler aromatic compounds; but we have worked more especially at the action of those substances on muscle and motor nerves, hoping in this way to lay a foundation for future researches on higher structures and more complex drugs.

Modifications in the Action of Drugs.

The action of drugs upon voluntary muscle is not always alike. It may be different in frogs and mammals; nay, more, it may differ in two species of frogs. It may be different in voluntary and involuntary muscle, and the involuntary muscular fibre of the heart may not react in quite the same way as that of the vessels, and the intestines may differ from both. Yet a general likeness can usually be discerned between the action of a drug on all kinds of muscular fibre, and it is precisely the fact that differences exist

which will give us most assistance in treatment, after we have once learned the causes of these differences. Caffeine usually, as I have said, contracts the muscles of the frog's legs, but sometimes it elongates them, and the same difference in its action is observed in the heart. Generally the heart stops in systole, but sometimes it stops in full diastole. In this respect the action of caffeine resembles that of digitalis.*

Complexity of the Heart.

In the heart we are not dealing with muscular fibre only, but with nerves and ganglia as well, and the effect of any drug upon this organ is the resultant of its action, not only upon all these structures in the heart, but also upon the medulla. Moreover, when we are dealing with the heart in connection with the blood-vessels the action becomes still more complex, for contraction or relaxation of the vessels will alter the resistance which the heart has to overcome. The problems we have to solve in looking for new cardiac tonics are, therefore, far from easy, but we may hope that patient investigation will solve them, and that we may ere long aid the sufferers from cardiac disease more efficiently than we can at present.

Direction in which to Look for Cardiac Tonics.

I have already pointed out that most drugs belonging to the class of cardiac tonics are also local anæsthetics, but all local anæsthetics do not appear to be cardiac tonics. Nevertheless, by looking through the class of local anæsthetics we may perhaps find some new cardiac tonics, and at any rate, it is worth while to try.

ACTION OF DRUGS ON THE BLOOD-VESSELS.

Our knowledge of the chemical nature of drugs which dilate the blood-vessels is somewhat greater than of those that contract them, for the agents which cause dilatation most markedly are of very simple chemical structure. They are, in fact, nitrites, or

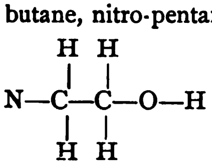
* Cf. Lauder Brunton "On Digitalis," pp. 96 and 108. London: Churchill. 1868.

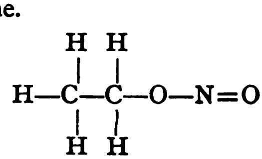
substances which yield nitrous acid in the blood, but all nitrites have not an equally powerful action, and the efficiency of the NO_2 depends to a great extent on the radical with which it is combined, and the mode in which this combination occurs. For the group NO_2 may be arranged thus: $—\mathrm{O}—\mathrm{N}{=}\mathrm{O}$, or $—\mathrm{N}\left\langle\begin{matrix}\mathrm{O}\\ | \\ \mathrm{O}\end{matrix}\right.$

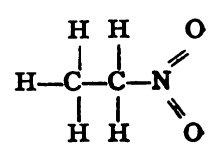
In each of these the nitrogen is trivalent. But it may be quinquevalent, in which case the group would be $—\mathrm{N}\begin{matrix}{/\!/}\mathrm{O}\\ {\backslash\!\backslash}\mathrm{O}\end{matrix}$. In nitrous compounds, it is probably—$\mathrm{O}—\mathrm{N}=\mathrm{O}$, while in nitric compounds it is probably $—\mathrm{N}\begin{matrix}{/\!/}\mathrm{O}\\ {\backslash\!\backslash}\mathrm{O}\end{matrix}$. We thus see that there may be considerable differences in the NO_2 groups, and the action of this group is determinable to a considerable extent by the alkyl to which it is joined and the manner in which the joining takes place.

Nitrites of Methyl, etc.

When we have the junction taking place through oxygen, the group NO_2 replacing (H) hydrogen in an alcohol, we obtain the nitrites of methyl, ethyl, propyl, butyl, amyl, and so on; but when we have the nitrogen directly united to carbon by one affinity, the group NO_2 replacing hydrogen (H) in a hydrocarbon, *e.g.*, methane, etc., or hydroxyl (HO) in an alcohol, we get the nitro-compounds, nitro-methane, nitro-ethane, nitro-propane, nitro-butane, nitro-pentane.


Ethyl alcohol.


Ethyl nitrite.


Nitro-ethane.

Action of Nitro-methane, etc.

These nitrous compounds appear to have less action on the vessels than the nitrites, and do not cause the same marked dilatation in them or consequent fall of blood pressure. They tend rather to produce narcosis, like the haloid compounds, chloroform, etc.

Amyl Nitrite.

Amyl nitrite has a rapid action, quickly occurring and quickly passing off, and since I first used it for angina pectoris in 1867 * its utility in the treatment of this disease has become almost universally recognised.

Other Nitrites.

While working in Ludwig's laboratory in 1869 on the action of this drug, I satisfied myself that other nitrites, and especially that sodium nitrite,† had a similar action. In 1876 Dr. Gresswell and I made some experiments, which we have not published, although we mentioned the research at the time in another paper upon the action of nitro-glycerine.‡ From these experiments it appeared that amyl nitrite had a more marked action than ethyl nitrite, but the next in the series, capryl nitrite, was less active than amyl. Recently the subject has again been taken up, and Cash and Dunstan have found that butyl nitrite is still more powerful than amyl, but the question now arises, Which butyl or amyl is it whose combination with NO_2 is most efficacious, that is to say, which acts most quickly and most powerfully?

Tertiary Amyl Nitrite.

According to Bertoni the nitrite obtained from tertiary amyl alcohol or ethyl-dimethyl-carbinol acts more powerfully and for a longer time than ordinary amyl nitrite. My assistants have tested it for me, and laboratory experiments showed that in animals,

* *Lancet*, July 27th, 1867. † Introduced as a remedy by Dr. Matthew Hay.

‡ Brunton and Tait on the Action of Nitroglycerine. St. Bartholomew's Reports, 1876. The severe headache it caused in us prevented us from using it in patients, but it was introduced into practice with great success by Dr. Murrell.

while it caused fall of blood pressure, it also produced vomiting. In one middle-aged patient, suffering from angina pectoris, it was not so efficacious as ordinary nitrite, and in him it produced vomiting; but in an old man it produced no vomiting, and gave more relief than other nitrites. It is possible that there may be a difference in the effect of the different nitrites in consequence of greater or less rigidity of the vascular walls. It is possible that where the vessels are not rigid ordinary amyl nitrite or iso-butyl nitrite may be best, but when the vessels are rigid a more prolonged action may be desirable, and in these nitro-glycerine and Bertoni's nitrite may be preferable.

Bright's Disease.

But there are other cases in which prolonged dilatation of the vessels is very desirable. First, in cases where the heart is weak and barely able to carry on the circulation; secondly, where the tension from the vessels is very high, and there is danger of rupture, as in cases of Bright's disease. In both of these it is highly probable that we may obtain better results with the nitrites of some of the higher alkyls than with any that have yet been employed. A series of experiments is also desirable on the action of nitro-butane, nitro-pentane, and other nitro-compounds in these cases.

Action of Drugs upon the Blood.

In addition to their power to dilate the vessels, nitrites have a very marked action upon the blood. When mixed with it they cause it to become of a chocolate colour, and they produce a similar change in it while it is still contained in the vessels of animals poisoned by nitrites. As Gamgee showed, nitrites, as it were, lock up oxygen in the hæmoglobin, so that blood which has been acted upon by them will not either take up or give off oxygen so readily as normal blood, but strong reducing agents will remove the oxygen, and then the reduced blood will combine with oxygen readily again. On this account nitrites do not arrest the respiration in the tissues in the same way as carbonic oxide, for when they have brought the animal to the verge of suffocation by locking up the oxygen in oxyhæmoglobin, the nitrous compound

becomes reduced, and the hæmoglobin then resumes its normal functions. A few inhalations of the nitrites, such as amyl nitrite, may thus produce asphyxial convulsions, but the animal recovers quickly and certainly unless the inhalation be maintained. The nitrite appears to behave to the oxygen of the blood corpuscles in somewhat the same way as the stopper of a bottle does to the liquid it contains, preventing anything from going out or into the bottle, but when sufficient force is applied to withdraw it, it no longer interferes with either exit or entrance. A similar effect is produced by nitro-glycerine and also by hydroxylamine. Nitrites must almost necessarily interfere with oxidation of the blood, and probably it is on this account that they give rise to the appearance of sugar in the urine. Nitrites, notwithstanding their marked effect upon hæmoglobin, do not destroy blood corpuscles, and consequently do not give rise to the presence of hæmoglobin in the urine; but a number of substances, more especially those belonging to the aromatic group, like toluylene-diamine, have this power, and an interesting question arises how far paroxysmal hæmoglobinuria may not really be a form of poisoning, due to the absorption of poisonous compounds of the aromatic series, and pernicious anæmia has been attributed by Sandoz* to poisoning by substances formed in the intestine and absorbed from it.

ACTION OF DRUGS ON THE LIVER.

For a long time the liver, notwithstanding its great size and its remarkable position, was regarded as having little functional importance, and was supposed merely to excrete bile, a fluid which plays quite a minor part in the digestive processes. But for some years back the liver has been gradually increasing in importance, and its functions are now recognised to be various in kind as well as most necessary to the organism.

Bile only a By-Product, although a Useful One.

The coal tar refuse of gas works is now utilised, at least in large towns, but even in small places gas continues to be made, although

* Sandoz, *Corr. Bl. f. Schweiz. Aerzte*, 1887.

the coal tar produced in the process cannot be worked up, and remains simply as refuse. In the same way the bile is certainly useful in the digestive process, preventing decomposition, accelerating peristalsis, and aiding the pancreatic juice to digest fats. But still it is, after all, to be regarded as a by-product of hepatic activity, bearing a similar relation to the glycogenic hæmolytic and other important functions of the liver that coal-tar does to the production of gas.

Dangers to Life.

The knowledge which we have gained during the last few years regarding the poisonous properties of some albuminous substances, and of the products which albumen yields when decomposed, makes it, as Mr. Darwin once said to me, a wonder that we are all alive considering how many poisonous substances are constantly formed in the intestine.

The Liver as a Gatekeeper.

Indeed, one can hardly see how life would continue long were it not that the liver has a position and function like the gatekeeper or porter of a town or castle in times of war, inspecting all comers and turning back those that are dangerous. It possesses a twofold power to prevent poisons entering the portal vein from passing into the general circulation, for it turns back some and destroys others. Some of them, such as lead, copper, mercury, and iron are simply arrested by it, and instead of passing into the general circulation are excreted by the bile, and finally ejected from the body. Some organic poisons, such as curara, appear also to be partly excreted in the same way. But the liver appears to have not only the power of excreting poisons but of actually destroying them, or, at any rate, converting them into non-poisonous compounds. Thus double the quantity of strychnine, veratrine, quinine, and morphine are required to kill an animal, if injected into the portal vein, as would be sufficient if injected into the jugular vein, while no less than three times the quantity of curara is requisite.* The liver exerts a similar power over peptones and

* Roger, *Action du Foie sur les Poisons.* Paris, 1887.

ptomaines, as well as over compounds of ammonia with weak acids, such as ammonium acetate, but chloride of ammonium is unaffected.

Uses of Glycogen in Regard to Poisons.

Organic poisons appear to have their activity lessened in the liver by combination with glycogen, for when animals are made to fast, the power of the liver to destroy the toxic actions of poisons gradually diminishes as the glycogen disappears. In cases where ptomaines are found in quantity in the intestine, Roger recommends such food to be given as will quickly supply glycogen, such as milk. He explains the usefulness of milk in uræmic poisoning in this way, while beef-tea in such cases simply increases the poison. It is possible that the peculiar symptoms of tremor, faintness, and even mental weakness which occur in some patients when fasting, and which are rapidly relieved by food, may be, in some degree due to the ptomaines formed in the intestine, and the relief by food may be explained by their destruction by the increased activity of the liver. At the same time we must remember that ptomaines—or, perhaps, we ought rather to say leucomaines—are formed in the tissues generally, and that an increase of glycogen in the blood may combine with poisonous products in the nerves and muscles, preventing them from exerting a poisonous action, and thus removing weakness, languor, or tremor due to them. The whole of this subject presents a fruitful field for further inquiry, and at present our knowledge is little more than sufficient to indicate how much there yet remains to be known.

Glycogenic Function of the Liver.

Another most important function of the liver is that of forming glycogen. It does this both from proteids and from carbohydrates, and thus acts, one might say, as the coal bunker of the body, storing up a reserve of nutriment to be utilised during the hours of fasting. But here, again, we meet with a curious action of some drugs.

Action of Ammonia.

Ammonia, as I have mentioned, is a poison, and so is ammonium

carbonate if injected into the jugular vein, but the poisonous activity of these substances is greatly diminished when they are injected into the portal vein. But this is not all. The liver actually converts these poisons into food, and when they are given to an animal, along with a non-nitrogenous diet, they increase the quantity of glycogen in the liver, and ultimately pass out in the form of urea, just as albumen would have done. Some amido-compounds, such as asparagine and glycocoll, have a similar action, but this is not shared by all the amido substances, for beef-tea and Liebig's extract contain a number of these, and yet neither seems to act in the same way as ammonia.*

Removal of Glycogen from the Liver.

Notwithstanding all the labour that has been expended in investigating the glycogenic function of the liver, it cannot be said that we clearly understand, even yet, the way in which glycogen is formed in the liver, or the way in which it disappears from it. Probably, a good deal of it is carried off by the blood in the form of sugar, and some also in the form of glycogen.

Action of Poisons upon Glycogen.

We have already seen that glycogen unites with some poisons, such as morphine, and with peptones, or other poisonous products of albuminous decomposition, so as to alter their properties and lessen their poisonous activity. We might therefore expect the converse to be the case, and look for them to exert an action upon glycogen, and perhaps render it less easily decomposed. We can readily understand on this supposition how the addition of a single egg, or piece of cheese, to a meal of bread-and-butter will increase its staying power, so that a person will be able, with this slight addition, to go on for four or five hours, instead of wanting another meal at the end of two. It would also explain the action of morphine in cases of diabetes. As Claude Bernard found that reflex dilatation of the hepatic artery would increase the transformation of sugar in the liver and induce diabetes, one was inclined

* Paul Bahlmann, *Inaug. Diss., Univ., Erlangen.* Münster, 1885.

to attribute the beneficial action of morphine or codeine to their sedative action on the nerve centres, preventing any irritation which might exist from affecting the hepatic vessels. But Mitchell Bruce has clearly shown that this is not the case, and that we must look to a direct action of morphine upon the liver itself for an explanation of its utility in diabetes.*

Glycosuria caused by Drugs.

There are a number of substances which will produce temporary glycosuria. Many of these are supposed to act by dilating the hepatic artery; for example, amyl nitrite, curara, ortho-nitro-propionic acid, methyl delphinine, chloroform, chloral hydrate, alcohol, and hydrocyanic acid. It is not improbable, however, that at least some of these may cause sugar to appear by lessening the normal processes of oxidation, by which it ought to be converted into carbonic acid. For carbonic oxide is a most powerful agent in producing glycosuria, and amyl nitrite, alcohol, and chloroform all tend to lessen oxidation. The most remarkable substance in producing glycosuria seems, however, to be phlorizin.† This substance, which is obtained from the root bark of apple trees, appears to have the power of preventing the organism from oxidising or otherwise utilising sugar. When dogs are kept without food for several days, but receive phlorizin all the time, the whole of the glycogen disappears both from the liver and the muscles; but if they are still kept without food, quantities of sugar appear in the urine, which can only be produced, so far as one can see, from the breaking up of the albuminous tissues of the body. In birds phlorizin causes glycosuria even after the liver has been extirpated.‡ Arsenic, antimony, and phosphorus all cause the glycogen to disappear from the liver,§ but they produce at the same time fatty degeneration,

* Mitchell Bruce. "Practitioner," July, 1888, vol. xli., p. 1. Lépine, *Arch. de Méd. Exper.*, tome 1, p. 56, has also shown that antipyrine retards the conversion of glycogen into sugar.

† Von. Mering, *Verh. d. h. Congress fur inn. Med.*, 1887.

‡ Minkowski and Thiel, *Arch. f. exp. Path. u. Pharm.*, Bd. 23, p. 142.

§ Salkowsky, *Virchow's Arch.* 34, p. 78.

whereas phlorizin appears simply to cause a general shrinking of the liver.*

Amount of Bile as an Index to Functional Activity in the Liver.

The secretion of bile, although it has attracted more attention than the other functions of the liver, is in itself of minor importance. But just as a stranger visiting a gas-factory in the country, where they could not use up their waste products, might judge by the amount of tar he saw about whether they had been making much gas or not, so from the secretion of bile we may draw important conclusions regarding another very important function of the liver, namely, its power to destroy blood corpuscles. Life appears to consist of a continual process of destruction and repair, and the blood forms no exception to the rule. Its vitality appears to be maintained by constant formation and destruction of blood corpuscles. Whether the corpuscles be actually broken up in the spleen, and their fragments carried to the liver, or whether they be destroyed in the liver itself does not at present concern us.

Relation between Blood-pigment and Bile-pigment.

At all events, it is in the liver, or rather perhaps we should say in the bile, that we find the remains of one of their most important constituents, hæmoglobin. Since Virchow pointed out the relationship between hæmatoidin and bile pigment, numerous researches have been made to show that hæmoglobin could be converted into bilirubin.

Hæmoglobinuria and Jaundice.

Thus, Kühne found that bile pigments appeared in the urine after the injection of hæmoglobin into the blood, and the same result has been observed after intravenous injection of substances which will dissolve corpuscles in the vessels, such as bile acids, large quantities of water, ether, chloroform, and phosphoric acid. In trying to repeat some of these experiments, many years ago, I

* Ueber d. Einfluss v. Giften a. d. Grösse d. Leberzellen. A. Neumann, *Inaug. Diss.* Berlin, 1888.

obtained a negative result,* and other observers have also failed. In place of bile pigment I found hæmoglobin,† and others have done the same, but Städeleman has cleared up the discrepancies. In his researches on toluylene-diamine he found that in some animals he obtained hæmoglobinuria, and in others jaundice. This jaundice was due to the fact that the bile ducts became plugged by bile so thick that it would not flow along an ordinary test tube, and much less through the hepatic ducts. The mode of action of the poison with which he experimented, as well as of chloroform, water, or bile acids injected into the circulation seems to be as follows: They break up the blood-corpuscles, liberating hæmoglobin; this is carried by the blood to the kidneys and liver, as well as to the other organs. In the kidneys it is partly excreted, giving rise to hæmoglobinuria. In the liver it is taken up by the hepatic cells and converted into bile pigment.

Hæmatogenous Jaundice.

In these experiments of Städeleman he observed that at first the whole quantity of bile is increased, solids as well as liquids, so that toluylene-diamine may be looked upon as a most powerful hepatic stimulant. Soon, however, the solids increase out of proportion to the fluid in the bile. It becomes thicker and thicker, until it will no longer flow along the ducts, and then, a part of it being absorbed from the biliary capillaries, jaundice is produced. These researches show that although all jaundice may be looked upon as of hepatic origin, yet the function of the liver is so much affected by the nature of the blood, that jaundice may occur in consequence of the destruction of red blood corpuscles, and the name of "hæmatogenous," as applied to such a form of jaundice, may therefore be justified.

* According to Filehne (*Virchow's Archiv.* cxvii., p. 415), the destruction of blood corpuscles by toluylene-diamine, phenylhydrazin, pyrodin, aniline derivatives, pyrogallol, potassium chlorate, glycerine, phosphorus, and arsenic, probably occurs in the liver and not in the blood generally, as in cases of poisoning by these substances hæmoglobin may be found in the bile when there is none in the urine.

† Lauder Brunton. "Sanderson's Handbook for the Physiological Laboratory," p. 499, footnote. London: Churchill. 1873.

Jaundice from Poisons.

One of the oldest observations on jaundice of this sort is probably that of Galen, that the skin becomes yellow in some persons after the bite of a viper. This is particularly interesting in relation to the possible causation of epidemic jaundice, or even of so-called catarrhal jaundice, in those cases where the catarrh is supposed to affect the bile ducts only, and there is no evidence of its extension to the intestine or stomach. The venom of poisonous snakes, both viperine and colubrine, paralyses both motor nerves and nerve centres, but the viperine poison differs from the colubrine in its effect upon the blood, which its deprives of its coagulating power, while at the same time it tends to destroy the red corpuscles. The researches of Weir-Mitchell, Reichert, Martin, and Wolfenden have shown that the poisonous substance in snake poison is not an acid or an alkaloid, but an albumose similar in its chemical reactions to the products of the ordinary digestion of albuminous foods in the stomach or intestine. It is only within the last few years that the poisonous properties of albumoses have been recognised, but poisons belonging to this class are now found to be pretty widely distributed.

Poisonous Blood in Fishes.

They occur, according to Martin, in the jequirity or abrus seed, and Mosso has recently found the blood of lampreys, eels, and probably of Murenidæ generally, to be poisonous from albuminous substances which it contains. The poisonous properties of albumoses are destroyed by boiling, and usually also by the simple process of digestion ; but if they should be taken in large quantity into the stomach they might be able to pass through the liver in sufficient quantity to prove injurious, and, if this be so, one can thus understand why Henry I. of England should have died after eating lampreys to excess.*

* Comedit carnes murenarum quæ semper ei nocebant, et semper eas amabat. Cum autem medicus hoc comedi prohiberet, non adquievit rex salubri consilio. . . . . Hæc igitur comestio, pessimi humoris illatrix et consimilium vehemens excitatrix, senile corpus letaliter refrigidans subitam et summam fecit perturbationem. Contra quod natura renitens excitavit febrem acutam ad impetum dissolvandum materiei gravissimæ. Cum autem restare nulla vi posset decessit rex magnus (*Hen. Huntingdon*, l. viii., c. 43).

Epidemic and Catarrhal Jaundice.

At present we are quite ignorant of the pathology of epidemic jaundice, or of those cases of catarrhal jaundice where yellowness is the only symptom, and it seems not improbable that both of these may be due to poisons of some sort absorbed from the intestine. I know of one case at least in which jaundice of this sort came on after eating ham which appeared to be tainted.

Acute Red Atrophy of the Liver.

In another case, which I saw only a few months ago, sudden illness came on a few hours after eating ham. I diagnosed the case as one of poisoning by ptomaines. Death occurred in a few days, and the post-mortem examination showed nothing to account for death, excepting that the liver was in a condition of red atrophy. This is a disease of whose pathology we are ignorant, and further researches must decide whether or not it may really be simply due to the effect of poisons on the organ.

NEW REMEDIES IN DISORDERS OF THE LIVER.

But an extended knowledge of pathology is not the only gain we may hope for from a thorough investigation of the action of drugs upon the liver; we may reasonably expect great additions to our power of treating its functional disorders, or even organic diseases. I have already mentioned the peculiar effect of ammonium salts upon the glycogenic function. Dr. Stewart's introduction of chloride of ammonium in hepatic abscess is a most important aid in the treatment of that disease. The biliary function appears to be modified in a remarkable way by many substances of the aromatic series which greatly increase the bile. It is a very remarkable thing that a great number of ptomaines belong to the class of compound ammonias or amines, and the remarkable action of toluylene-diamine appeared to me to indicate the necessity for ascertaining, if possible, what effect would be produced on the liver by bodies of the aromatic series, free from nitrogen, as compared with the effect of similar bodies combined with ammonia. At my suggestion Dr. Collins made a number of experi-

ments with toluene and toluylene-diamine in my laboratory, and found that both these substances greatly increased the flow of bile. Not feeling quite certain what effect toluylene-diamine and allied bodies might have upon patients, I felt a little chary of using them until I should obtain fuller knowledge of their mode of action. In order to be ready, however, to use them as soon as I had acquired sufficient knowledge, I asked Messrs. Burroughs and Wellcome to prepare me some tabloids and capsules containing toluene and toluylene-diamine. This they kindly did, and a gentleman to whom Dr. Collins had mentioned the existence and probable use of the tabloids, tried them upon his patients with good success, as he informs me.

Vegetable Cholagogues.

Most of the vegetable hepatic stimulants, iridin, euonymin, and aloes, belong to the aromatic series, although we do not know their chemical structure. Much benefit is frequently obtained by their use in so-called "biliousness," and we may reasonably expect that a full knowledge of the mode of action and chemical structure of the vegetable cholagogues will enable us, not only to apply them more judiciously, but to modify their structure, and consequently their action in various directions, to suit our wants. It is almost certain, also, that we shall obtain a very large series of new bodies which may act upon the liver, either as stimulants or as depressants, increasing or diminishing the formation of bile, and affecting the other functions of the organ, which I have already mentioned. The frequency with which functional hepatic disorder occurs, and the great discomfort which it occasions, not only to the sufferer, but to his friends, and even to the community at large, renders it most desirable that efficient modes of treatment should be discovered.

Methods of Searching for New Hepatic Remedies.

The search after new remedies has hitherto been conducted almost entirely in two ways: first, by the administration of drugs to patients, and, second, by the administration of drugs to animals,

and ascertaining their action in altering the quantity and quality of the bile secreted, as well as by making a chemical analysis of the liver itself so as to ascertain whether the amount of glycogen and fat has been altered by the drug. According to Ellenberger and Baum, who experimented on horses, the hepatic

Fig. 28.

Fasting Liver. Rabbit 6 weeks old. Last food, 18½ hours before death (after Sheridan Delépine).

cell when in action is larger, has a sharper contour, has a net-like arrangement of its protoplasm, and contains more granules which stain with eosine,* and fewer pigment granules than the cell when at rest. This active condition of the cell occurs during digestion, but it may be produced independently of digestion by such drugs as pilocarpin, muscarin,

* Cf. "Action of Eosine," p. 9.

and aloes. A similar but less powerful action is exerted by salicylate and benzoate of sodium and by rhubarb. On the other hand, atropine arrests the activity of the liver, so that the hepatic cells appear to be completely at rest, even in the very middle of the digestive process. A similar but less powerful action is exerted by ammonium chloride, sulphate of magnesium, and calomel.

Fig. 29.
Active Liver. Rabbit six weeks old. Killed six hours after meal (after Sheridan Delépine).

Copper and lead also arrest the hepatic activity, but when they are given for a time they produce fatty degeneration of the cells and accumulation of bile in them. The action of a very large number of substances on the liver cells has been investigated by Alfred Neumann under Ehrlich's direction; and many belonging to the aromatic series have been found to produce enlargement

of the hepatic cells. Amongst these are cocaine, cou marin, aceto phenone, azobenzine, dibromazobenzene, dimethylparaphenylen-diamine sulphate, martius yellow, orthonitrophenyl, propionic acid, paraoxybenzaldehyde, paratoluidin, phenanthroquinone, and phenylthio-urea.

Dr. Sheridan Delépine has kindly examined for me the changes

Fig. 30.
Action of Atropine on an Active Liver. Rabbit six weeks old. Last food, $5\frac{1}{2}$ hours before death. Injection of $\frac{1}{80}$th gr. atropine 3.2 hours before death (after Sheridan Delépine).

which the hepatic cells in the rabbit undergo under the action of atropine, pilocarpine, and toluene. It will be seen from the accompanying figures that the effect of atropine and pilocarpine on the liver of the rabbit resembles that which Ellenberger and Baum have described as occurring in the horse.

The effect of toluene is very peculiar. The outline of the cells becomes sharp, but the cells become small and the blood vessels large, so that the liver is congested. The bile also appears to be expelled from the liver, for the blood corpuscles in the vessels are not destroyed, while they usually are dissolved by the bile.

This subject is one of the greatest possible practical interest,

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Action of Pilocarpine on a Fasting Liver. Rabbit six weeks old. Last food, 17½ hours before death. Injection of ½ gr. pilocarpine 1½ hours before death (after Sheridan Delépine).

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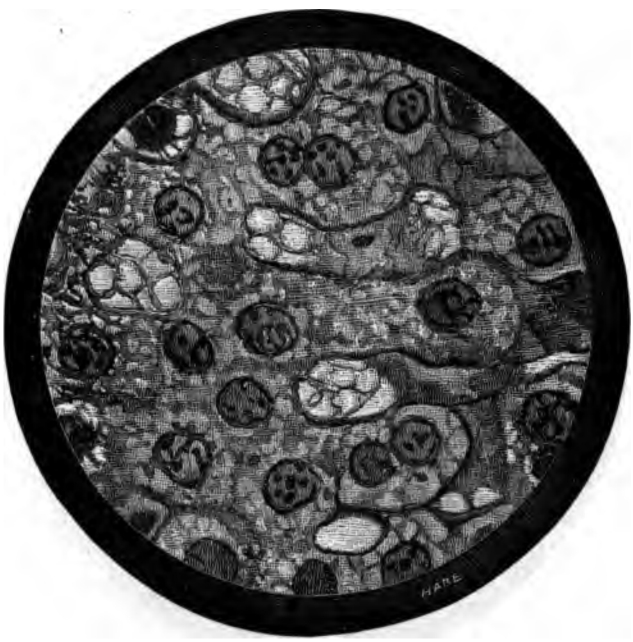

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As I mentioned in my first lecture, the latest development of pharmacology is the "pharmacology of the cell;" and to it we must look for the fullest information regarding the action of remedies, whatever be the class to which they belong.

Time will not allow me to enter upon the relations between the chemical structure of remedies and their action upon other glands

Fig. 33.

Action of Toluene on Fasting Liver. Rabbit six weeks old. Last food, 20 hours before death. Toluene, 1 minim, 4¾ hours before death (after Sheridan Delépine).

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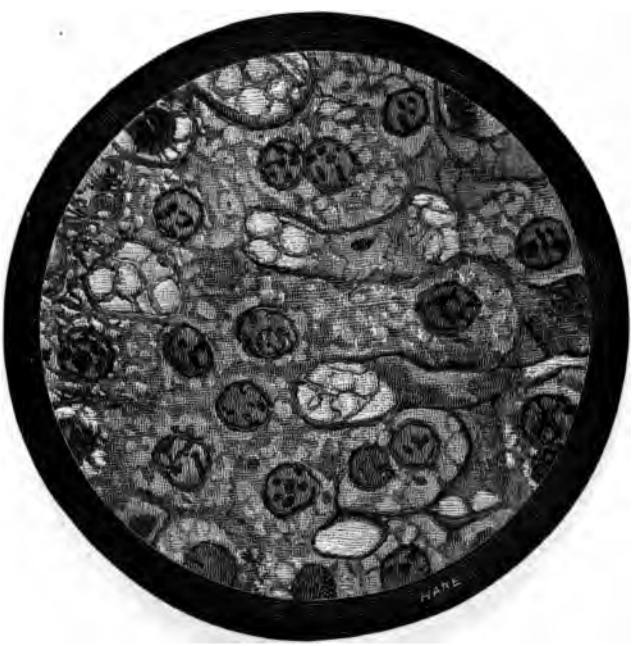

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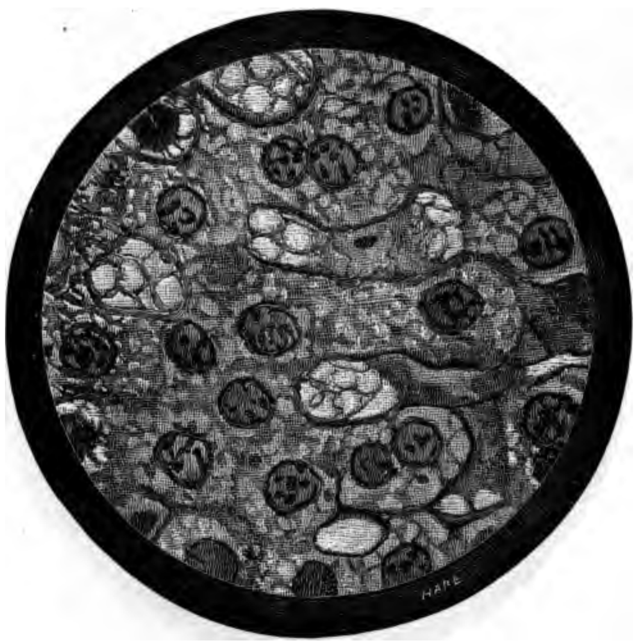

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